CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-515

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA 21-515
WELLBUTRIN XL

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-515
Brand Name:	Wellbutrin XL
Generic Name:	Bupropion HCl
Type of Dosage Form:	Extended Release Tablet
Strengths:	150 mg, 300 mg
Indications:	Major Depressive Disorder
Type of Submission:	NDA Response to Approvable Letter
Sponsor:	GlaxoSmithKline
Submission Date:	July 3, 2003
OCPB Division:	DPE-I
OND Division:	Division of Neuropharmacological Drug Products HFD-120
OCPB Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCPB Team Leader:	Ramana Uppoor, PhD

1 Executive Summary

This review evaluates the Sponsor's response to the recommendations made by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) in the approvable action letter for NDA 21-515.

In the review of the original NDA (see OCPB review of 5/12/03), based entirely on bioequivalence studies, the Office of Clinical Pharmacology and Biopharmaceutics recommended the following:

- A change in the *in vitro* dissolution specification
- A literature review and adverse event review to evaluate the potential for drug interactions with CYP2B6 substrates/inhibitors, since *in vitro* studies have suggested that some SSRIs and some protease inhibitors inhibit CYP2B6-mediated hydroxylation of bupropion.
- Specific revisions of the proposed label's text, including revisions regarding CYP2B6-mediated drug interactions

The Sponsor has provided responses as follows:

- The Sponsor has provided justification for broadening the specification at 4 hours, and proposes the following dissolution specifications for WELLBUTRIN XL 150 and 300 mg tablets:

  2 hours:
  4 hours: [redacted]
  8 hours:
  16 hours:

The Office of Clinical Pharmacology and Biopharmaceutics agrees with the Sponsor's proposed dissolution specifications, and recommends that those specifications be adapted.

- The Sponsor has provided a literature review and adverse event review to evaluate the potential for drug interactions with CYP2B6 substrates/inhibitors. The Sponsor suggests that clinically significant interactions are unlikely. Their rationale is that 1) bupropion is metabolized by multiple pathways so that other pathways can compensate, 2) multiple P450 isozymes catalyze the hydroxylation of bupropion to hydroxybupropion, and 3) low unbound plasma concentrations of these highly protein bound substrates/inhibitors relative to the *in vitro* IC_{50} make the *in vitro* observations clinically insignificant. In addition the Sponsor suggests that neither the case reports in the literature nor the case reports in the Sponsor's adverse events database support a clinically significant CYP2B6-mediated drug interaction.

  However, although bupropion is metabolized by multiple pathways to multiple metabolites so that other metabolites may be formed if formation of hydroxybupropion is blocked, the contributions to efficacy and safety of the various other metabolites, at concentrations which cannot be predicted at this point, is unknown. In addition the actual role of other P450s in catalyzing the hydroxylation of bupropion if CYP2B6 were blocked in humans is unknown. The literature is unclear as to how to extrapolate data from *in vitro* binding studies with drugs that are highly protein bound and the effect of protein binding on P450 inhibition in humans is difficult to predict. Finally, while the case reports do not necessarily confirm clinically relevant drug interactions, they do not rule out the possibility.

  The *in vitro* studies suggest that specific SSRIs as well as specific protease inhibitors can inhibit CYP2B6-mediated hydroxylation of bupropion. However, the clinical significance is unknown.

- The Sponsor has made all of the labeling changes that were recommended by the OCPB, [redacted] The OCPB recommends that the labeling reflect this interaction.

1.1 Recommendations and Comments to Sponsor

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has the following recommendations.

1) The proposed *in vitro* dissolution specification is acceptable.
2) The OCPB recommends some revisions of the proposed label's text regarding CYP2B6-mediated drug interactions with SSRIs and protease inhibitors. (Please refer to Section 3.2.3).
3) If the Sponsor does not wish to include [redacted]

Please forward the comments above and the labeling comments in Section 3.2.3 to the Sponsor. Please also forward the following comment to the Sponsor:

In the approvable letter, the Office of Clinical Pharmacology and Biopharmaceutics recommended that in the future, the Sponsor should adhere to the practice of using [redacted] for each dissolution profile. The Sponsor has requested confirmation of the information provided in the teleconference of July 2, 2003 regarding this recommendation. It should be noted that this is not necessary for routine QC testing (i.e. standard USP stages apply). This recommendation refers to the number of tablets that should be tested for the data that should be submitted on pivotal biobatches in the NDA in support of setting the dissolution specification.

Sally Usdin Yasuda, MS, PharmD
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana Uppoor, PhD
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Summary of Clinical Pharmacology and Biopharmaceutics Findings

4.1 Background

WELLBUTRIN XL tablets are bupropion hydrochloride extended release tablets for once daily administration for major depressive disorder. WELLBUTRIN XL Tablets (NDA 21-515, August 26, 2002) received an approvable action letter on June 24, 2003, to which the present submission is a complete response.

The Clinical Pharmacology and Biopharmaceutics Recommendations for that submission were that the submitted data were acceptable, pending the outcome of the DSI inspection report of the pivotal bioequivalence study (AK1BIOVAIL2543). Based on the DSI report and further review dated 6/20/03, the study was considered acceptable. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommended the following:

- A change in the *in vitro* dissolution specification
- A literature review and adverse event review to evaluate the potential for drug interactions with CYP2B6 substrates/inhibitors.
- Specific revisions of the proposed label's text, including revisions regarding CYP2B6-mediated drug interactions

The Sponsor has submitted a complete response to the approvable letter. The response to the Clinical Pharmacology and Biopharmaceutics recommendations will be addressed here.

4.2 Current Submission

3.2.1 Dissolution Specifications

- *Is the proposed dissolution specification acceptable?*

The Office of Clinical Pharmacology and Biopharmaceutics recommended that the specification be changed to the following:

2 hours:
4 hours: [redacted]
8 hours:
16 hours:

This recommendation was based on an approximate 10% deviation from the mean dissolution profiles from bioavailability lots. This reflected the Guidance for Industry "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations" that states when dissolution specifications are set without an

IVIVC, the recommended range at any dissolution time point specification is +/- 10% deviation from the mean dissolution profile from bioavailability lots, and although deviations from that range can be accepted, the range should not exceed [redacted]

The Sponsor has proposed a shift in the specification range at 4 hours to [redacted] reflecting the different dissolution profiles of the 150 mg and 300 mg strengths at that time. The mean % dissolved at 4 hours is [redacted] for the 150 mg strength tablets and [redacted] for the 300 mg strength tablets. A range of ± 25% would be approximately [redacted] and [redacted], for the 150 mg and 300 mg strengths, respectively. To allow the same dissolution specifications for both strengths of tablets, the proposed range of [redacted] at 4 hours is acceptable. The Office of Clinical Pharmacology and Biopharmaceutics recommends that the specification be changed to the following:

2 hours:
4 hours: [redacted]
8 hours:
16 hours:

In addition, in the approvable letter, the Office of Clinical Pharmacology and Biopharmaceutics recommended that in the future, the Sponsor should adhere to the practice of using [redacted] for each dissolution profile. The Sponsor has requested confirmation of the information provided in that teleconference of July 2, 2003 regarding this recommendation. It should be noted that this is not necessary for routine QC testing (i.e. standard USP stages apply). This recommendation refers to the number of tablets that should be tested for the data that should be submitted on pivotal biobatches in the NDA in support of setting the dissolution specification.

3.2.2 Evaluation of the Potential for Drug Interactions

According to the label for WELLBUTRIN SR (extended to the proposed labeling for WELLBUTRIN XL), *in vitro* studies suggest that bupropion is primarily metabolized to hydroxybupropion by CYP2B6. The results of recent *in vitro* studies[1,2] suggest that several SSRIs and antiretroviral drugs may inhibit the hydroxylation of bupropion by CYP2B6. Specifically, the reviewer identified two publications in the literature evaluating *in vitro* the potential for P450-mediated drug interactions with bupropion. Hesse et al[2] evaluated potential drug interactions with other antidepressants in human liver microsomes and reported a mean IC_{50} value for paroxetine of approximately 1.6 μM. Sertraline, norfluoxetine, and fluvoxamine also inhibited bupropion metabolism with mean IC_{50} values of 3.2, 4.2, and 6.1 μM, respectively. Hesse et al[1] have also reported inhibition of bupropion hydroxylation in human liver microsomes by nelfinavir, ritonavir, and efavirenz with mean IC_{50} values of 2.5, 2.2, and 5.5 μM respectively.

The Office of Clinical Pharmacology and Biopharmaceutics recommended that the Sponsor conduct a thorough search of the literature as well as adverse event reports for bupropion to evaluate the potential for pharmacokinetic and/or pharmacodynamic

(adverse event) drug interactions with bupropion and an inhibitor/substrate such as paroxetine, sertraline, fluvoxamine, norfluoxetine, efavirenz, ritonavir, and nelfinavir.

- *Will the in vitro studies predict a clinically significant drug interaction?*

The Sponsor suggests that clinically significant interactions are unlikely. Their rationale is that 1) bupropion is metabolized by multiple pathways so that other pathways can compensate, 2) multiple P450 isozymes catalyze the hydroxylation of bupropion to hydroxybupropion, and 3) low unbound plasma concentrations of these highly protein bound substrates/inhibitors relative to the *in vitro* IC_{50} make a clinically significant interaction unlikely.

Although bupropion is metabolized by multiple pathways to multiple metabolites so that other metabolites may be formed if formation of hydroxybupropion is blocked, the contributions to efficacy and safety of the various other metabolites, at concentrations which cannot be predicted at this point, is unknown. In addition the actual role of other P450s in catalyzing the hydroxylation of bupropion if CYP2B6 were blocked is unknown. (Greenblatt et al[2] evaluated the hydroxylation in human liver microsomes, and reported that the hydroxylation is mediated almost exclusively by CYP2B6). Finally, the literature is unclear as to how to extrapolate data from *in vitro* binding studies with drugs that are highly protein bound. For example, paroxetine has a free fraction of 0.05, has an IC50 of approximately 2.54 μM for inhibiting CYP2D6 in human liver microsomes in vitro (determined under similar experimental conditions as reported by Greenblatt et al to evaluate paroxetine's effect on bupropion hydroxylation in which the IC50 was reported to be approximately 1.6 μM).[3] Paroxetine, although it is highly protein bound, resulted in more than a 3-fold increase in Cmax, AUC and t1/2 of atomoxetine, a CYP2D6 substrate when paroxetine was given at a dose of 20 mg daily, achieving paroxetine Cmax concentrations of approximately 39.5 ng/ml.[4] Thus, the effect of protein binding on P450 inhibition in humans is difficult to predict.

Finally the Sponsor cites, as evidence for the importance of other metabolic pathways, an abstract by Brockmoller et al in which known variants of CYP2B6 did not appear to result in outliers in terms of bupropion pharmacokinetics.[5] The authors concluded that there is no evidence of "bupropion poor metabolizer phenotypes or genotypes". In addition, the study apparently evaluated only bupropion pharmacokinetics, and did not include metabolites. Thus the results of this citation cannot be used to conclude that CYP2B6 interactions are unlikely to be clinically significant.

The following table, provided by the Reviewer, uses total, rather than unbound, plasma concentrations (provided by Sponsor) relative to the IC_{50} values for inhibition of bupropion hydroxylation as reported in the literature[1,2].

Inhibitor	C_{max} (ng/ml)	Molecular Weight	IC_{50} (μM)	IC_{50} (ng/ml)	C_{max}/IC_{50}
Nelfinavir[a] (free base)	[redacted]	567.79	2.5	1419	2.82
Ritonavir	[redacted]	720.95	2.2	1586	2.33
Efavirenz		315.68	5.5		2.35
Nefazodone	[redacted]	506.5	25.4	12865	0.25
Sertraline		342.7	3.2	1097	0.17
Paroxetine	[redacted]	374.8	1.6	600	0.10
Norfluoxetine	[redacted]	331.8	4.2	1394	0.19
Fluvoxamine		318.353	6.1	1942	0.28

[a]Using the molecular weight for the mesylate salt [redacted] the C_{max}/IC_{50} is 2.41
[b]Concentration expressed as μM

The nature of this inhibition has not been determined. If it is competitive (and using a substrate concentration *in vitro* that was somewhat less than the K_m for hydroxylation as in the published in vitro studies[1,2]), the IC_{50} would be 1-2 times greater than that of the K_i value, resulting in C_{max}/K_i values even greater than those shown for the C_{max}/IC_{50} values in the table above. Using the guideline that interactions would likely occur if the C_{max}/K_i is greater than 1, and possible if the C_{max}/K_i is between 0.1 and 1, these *in vitro* studies suggest the potential for a CYP2B6-mediated drug interaction.[6]

In summary, there is *in vitro* evidence to show that bupropion hydroxylation is mediated by CYP2B6 and can be inhibited by ritonavir, efavirenz, nelfinavir, as well as by sertraline, paroxetine, norfluoxetine, and fluvoxamine. No clinical studies have been performed to evaluate this finding, and therefore the clinical relevance is unknown.

- *Is there data in the literature to rule out clinically significant drug interactions between bupropion and either SSRIs or protease inhibitors?*

The Sponsor has conducted a literature search evaluating concomitant use of bupropion and various SSRIs and has found that these combinations are reportedly well tolerated, with adverse events similar to those associated with each monotherapy. These studies were not designed to evaluate drug interaction effects on bupropion exposure. The Sponsor cites 3 case reports in the literature describing adverse events during combination therapy with bupropion and either an SSRI, including three reports of seizure, for which in all cases one or both agents were discontinued or dosages were decreased and adverse events resolved. It is difficult to determine whether P450-mediated drug interactions played a role in these adverse reactions. However, the Sponsor has provided a reference to 1 abstract[7] in which 13 patients who were on bupropion at doses of 150-450 mg/day had serum drawn before and after 12-60 days of

concomitant treatment with either sertraline or fluoxetine. One patient's bupropion concentration rose from [redacted]. No other details are available.
The Sponsor cites a case series in the literature describing the combination of bupropion with nelfinavir, ritonavir, or efavirenz given to 10 patients, eight of whom had predisposing risk factors for seizures. No seizures were reported.

In summary, there has not been a systematic evaluation of drug interactions with bupropion and protease inhibitors or SSRIs reported in the literature. There were several reports of seizures, as well as 1 case in which a pharmacokinetic interaction occurred. Thus there is not enough information to draw a conclusion about the clinical relevance of potential CYP2B6-mediated drug interactions.

- *Do the results of the Sponsor's adverse event database rule out the likelihood of clinically significant drug interactions between bupropion and either SSRIs or protease inhibitors?*

The Sponsor has provided a summary of case reports in the adverse event database of Global clinical Safety and Pharmacovigilance. These included all indications and formulations for the use of bupropion up to and including May 31, 2003. Particular attention was given to reports of seizures and those will be addressed here. Cases of seizures when bupropion was used with SSRIs were reported as follows. Plasma concentration data was not available. For paroxetine, there were seizures in 6 cases reported as suspected drug interactions, although the role of concomitant use was unclear in these cases. There were 42 other cases in which seizure was reported in patients on bupropion and paroxetine concomitantly. In 9 of those, time to onset was reported and was typically after addition of bupropion to pre-existing paroxetine therapy. In 9 cases, other risk factors for seizure were reported. For fluoxetine there were 6 cases reported as possible interactions, in which seizure was reported. These occurred either shortly after stopping fluoxetine (1), shortly after increasing the bupropion dose to 450 mg on a stable dose of fluoxetine (1), shortly after adding fluoxetine to a stable regimen of bupropion with possible involvement of paroxetine (1), or with an unknown time course of co-administration. There were 91 other cases in which seizure was reported in patients on bupropion and fluoxetine concomitantly. In more than half of those cases, seizure occurred following overdose of either bupropion or fluoxetine, in the setting of other medications known to lower seizure threshold, or in patients with risk factors for seizure, with insufficient information in the remaining cases. For fluvoxamine, there were 5 cases reported as possible interactions, in which seizure was reported. In one case the time course for co-administration was not clear, in the others it occurred after fluvoxamine was added to the bupropion regimen, after adding bupropion to the regimen, or after the dose of fluvoxamine was increased. There were 8 other cases in which seizure was reported in patients on bupropion and fluvoxamine concomitantly. In 6 of those cases the patients had other risk factors for seizures, and 1 case occurred in a breastfeeding infant of a mother receiving bupropion and fluvoxamine, with apparently confounding factors in the other case. For sertraline, there was one case reported as a possible interaction in which a seizure occurred after adding sertraline to a regimen of bupropion. There were 33 other cases of seizures in patients taking sertraline with bupropion in which bupropion

was reported as the suspect drug. There is no further information provided regarding those reports.

Similarly there have been case reports of adverse events in patients taking bupropion with nelfinavir, ritonavir, or efavirenz. There was one case report of myclonia when bupropion was given with nelfinavir, and although the reporter stated that there were laboratory results to indicate a possible pharmacokinetic interaction, the laboratory values were not provided in the report. There was 1case of seizure in a patient taking bupropion with ritonavir, although blood levels were not available. There were no cases of seizures reported with the concomitant use of bupropion and efavirenz.

In summary, although there are several case reports in the Sponsor's database of seizures when bupropion was given with SSRIs or protease inhibitors, the available information cannot be used to determine whether a pharmacokinetic drug interaction occurred, and cannot be used to rule out the possibility of clinically significant CYP2B6-mediated drug interactions.

3.2.3 Recommended Labeling Changes

The Office of Clinical Pharmacology and Biopharmaceutics previously recommended some revisions in the proposed label text. All of the proposed changes were made with the exception of the addition of information regarding the in vitro studies regarding CYP2B6-mediated drug interactions. Based on the discussion in section 3.2.2 above, and in agreement with the Guidance for Industry entitled "In Vivo Drug Metabolism/Drug Interaction Studies – Study Design, Data Analysis, and Recommendations for Dosing and Labeling" that has specific labeling recommendations when an *in vitro* interaction has been demonstrated, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommends inclusion of that information in the labeling in paragraph 2 (beginning at line 382) of the Drug Interactions section of the label. The recommended change language is as follows (OCPB changes in the labeling are highlighted):

"Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between WELLBUTRIN XL and drugs that are substrates or inhibitors of the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir, ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been performed to evaluate this finding. The threohydrobupropion metabolite.....

4.3 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the proposed changes in the dissolution specifications acceptable.

The OCPB does not find the proposed changes in the labeling regarding the potential for drug interactions acceptable, and recommends changes that reflect this potential, identified in section 3.2.3 above. Please forward the labeling comment to the Sponsor.

5 References

1. Hesse LM, von Moltke LL, Shader RI, Greenblatt DJ. Ritonavir, efavirenz, and nelfinavir inhibit CYP2B6 activity in vitro: Potential drug interactions with bupropion. Drug Metab Dispos 2001; 29(2):100-102.

2. Hesse LM, Venkatakrishnan K, Court M, von Moltke LL, Duan SX, Shader RI et al. CYP2B6 Mediates the In Vitro Hydroxylation of Bupropion: Potential Drug Interactions with Other Antidepressants. Drug Metab Disp 2000; 28(10):1176.

3. Bertelsen KM, Venkatakrishnan K, von Moltke LL, Obach RS, Greenblatt DJ. Apparent mechanism-based inhibition of human CYP2D6 in vitro by paroxetine: comparison with fluoxetine and quinidine. Drug Metab Dispos 2003; 31(3):289-293.

4. Belle DJ, Ernest S, Sauer J-M, Smith BP, Thomasson HR, Witcher JW. Effect of potent CYP2D6 inhibition by paroxetine on atomoxetine pharmacokinetics. J Clin Pharmacol 2002; 42:1219-1227.

5. Brockmoller J, Kirchheiner J, Klein C, Sasse J, Roots I. Variability of bupropion pharmacokinetics in relation to amino acid polymorphism in CYP2B6. Clin Pharmacol Ther 2003; 73(2):P56.

6. Bjornsson TD, Callaghan JT, Einolf HJ, Fischer V, Gan L, Grimm S et al. The conduct of in vitro and in vivo drug-drug interaction studies: a Pharmaceutical Research and Manufacturers of America (PhRMA) perspective. Drug Metab Dispos 2003; 31(7):815-832.

7. Gerner RH, Kaufman KR, Rosen R. Seizures associated with bupropion and SSRIs and serum levels. Biol Psychiatry 1998; 43:101s.

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/s/

Sally Yasuda
7/30/03 11:19:35 AM
BIOPHARMACEUTICS

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BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-515	
Brand Name:	Wellbutrin XL	
Generic Name:	Bupropion HCl	
Type of Dosage Form:	Extended Release Tablet	
Strengths:	150 mg, 300 mg	
Indications:	Major Depressive Disorder	
Type of Submission:	New/3S	
Sponsor:	GlaxoSmithKline	
Submission Date:	August 26, 2002 December 18, 2002 January 24, 2003 February 11, 2003	April 15, 2003 April 17, 2003
OCPB Division:	DPE-I	
OND Division:	Division of Neuropharmacological Drug Products HFD-120	
OCPB Reviewer:	Sally Usdin Yasuda, MS, PharmD	
OCPB Team Leader:	Ramana Uppoor, PhD	

1 Executive Summary

This NDA review evaluates *in vivo* and *in vitro* data regarding WELLBUTRIN XL (extended release) tablets (150 mg and 300 mg) to be indicated for major depressive disorder. The to-be-marketed tablets were used in the pharmacokinetic studies. This NDA is entirely based on bioequivalence studies. Clinical studies were not conducted on these tablets.

- Bioequivalence was demonstrated for bupropion metabolites between the highest strength WELLBUTRIN XL tablet (300 mg) and the approved immediate release product WELLBUTRIN given as 100 mg three times daily. Although bioequivalence could not be demonstrated for the parent compound (for C_{min} only; C_{max} and AUC met bioequivalence criteria), consideration should be given to the active metabolites, since they are responsible for more than 90% of the exposure following administration of bupropion. Therefore it is reasonable to suggest that the two products were comparable in exposure.

  It should be noted that although comparable exposure was demonstrated, there are differences in the shapes of the curves for bupropion in the WELLBUTRIN XL formulation compared with immediate release formulation. The clinical relevance of these differences cannot be predicted based on the pharmacokinetics. However, the comparable exposure and the role of the metabolites in the exposure and pharmacologic activity support the approval of the WELLBUTRIN XL formulation. Of note, for WELLBUTRIN SR, although there were also differences in the shapes of the plasma concentration curves compared to WELLBUTRIN IR, a clinical trial demonstrated efficacy of WELLBUTRIN SR in maintaining antidepressant response.

- Dosage strength equivalence was demonstrated between the 150 mg and 300 mg strengths of WELLBUTRIN XL.

- There is no appreciable effect of food on exposure to bupropion or its metabolites when WELLBUTRIN XL (300 mg) is given with a high fat meal.

In addition, recent data in the literature suggest that several SSRIs (sertraline, paroxetine, and fluvoxamine as well as norfluoxetine) and several antiretroviral drugs (ritonavir, efavirenz, and nelfinavir) inhibit the hydroxylation of bupropion *in vitro*. The Office of Clinical Pharmacology and Biopharmaceutics recommends that the label be revised with respect to the potential for CYP2B6-mediated interactions.

1.1 Recommendations and Comments to Sponsor

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the submitted data in NDA 21-515 for WELLBUTRIN XL acceptable, pending the outcome of the DSI inspection report of the pivotal bioequivalence study AK1BIOVAIL2543. The OCPB recommends some revisions of the proposed label's text (please refer to Section 5).

1) The proposed *in vitro* dissolution method is acceptable. The OCPB recommends that the specification be changed to the following:

2 hours: [redacted]
4 hours:
8 hours: [redacted]
16 hours:

In addition, it should be noted that the Sponsor has not consistently used [redacted] tablets for each time point in the dissolution profiles. In the future, the Sponsor should adhere to the practice of using [redacted] for each dissolution profile.

2) Bupropion is hydroxylated by CYP2B6. Recently, *in vitro* studies have identified more substrates and inhibitors of CYP2B6, and the results of recent *in vitro* studies suggest that several SSRIs and antiretroviral drugs may inhibit the hydroxylation of bupropion by CYP2B6. It would be useful to characterize the requirement for dosing modifications, if necessary, when such drugs are given with bupropion. Therefore we recommend that you conduct a thorough search of the literature as well as adverse event reports for bupropion to evaluate the potential for pharmacokinetic and/or pharmacodynamic (adverse event) drug interactions with bupropion and an inhibitor/substrate such as paroxetine, sertraline, fluvoxamine, norfluoxetine, efavirenz, ritonavir, and nelfinavir. Based on literature results, an *in vivo* drug-drug interaction study may be necessary.

Please forward the comments 1 and 2 above and the labeling comments in Section 5 to the Sponsor.

Clinical Pharmacology & Biopharmaceutics Required Interdivision Briefing:
May 9, 2003
Attendees: Mehul Mehta, John Hunt, Tom Laughren, Bob Levin, Sally Yasuda, Ramana Uppoor, Roshni Ramchandani

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Reviewer, Neuropharmacological Drug Section, DPE I
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HFD-860 /DD DPEI/M. Mehta, C. Sahajwalla

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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

3.1 Background

WELLBUTRIN XL tablets are extended release tablets for once daily administration that contain bupropion hydrochloride. Bupropion is currently available as an antidepressant medication in other formulations, an immediate release tablet that is given 100 mg three times daily, and a sustained release (SR) formulation that is given twice daily.

The mechanism of action of bupropion as an antidepressant is unknown but is thought to be mediated by noradrenergic and/or dopaminergic mechanisms. According to the Sponsor it inhibits neuronal reuptake of norepinephrine and dopamine and does not inhibit monoamine oxidase.

According to the WELLBUTRIN SR label, bupropion and its metabolites display linear kinetics with chronic administration of 300 to 450 mg/day. Bupropion has an elimination half-life of approximately 22 hours. It is extensively hepatically metabolized. It has three active metabolites, hydroxybupropion, threohydrobupropion (bupropion threoamino alcohol), and erythrohydrobupropion (bupropion erythroamino alcohol) that account for approximately 90% of the exposure following administration of bupropion. Its P450-mediated metabolism is primarily via CYP2B6.

3.2 Current Submission

The present NDA (21-515) has been submitted to support the approval of WELLBUTRIN XL for the treatment of major depressive disorder. The strengths are 150 mg and 300 mg. The proposed target dose is 300 mg/day given once daily. It is recommended that dosing begin at 150 mg/day. The maximum recommended dose is 450 mg/day.

Two studies were submitted but not reviewed by OCPB as they were pilot studies evaluating several different formulations of WELLBUTRIN XL tablets. These studies were:

- AK1BIOVAIL2526 - Pilot bioequivalence of two candidate formulations
- AK1BIOVAIL2544 - Bioequivalence of discontinued formulation

In addition, Study OHB10001, a positron emission tomography study to evaluate dopamine transporter occupancy was reviewed, but not utilized in the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) evaluation of the data submitted to support this NDA for this once a day formulation.

The following clinical pharmacology studies have been submitted and reviewed:

- AK1BIOVAIL2543 - Steady state study of the bioequivalence of WELLBUTRIN XL 300 mg once daily and WELLBUTRIN 100 mg immediate release given 100 mg three times daily
- AK1BIOVAIL2571 - Dosage strength equivalence study comparing 150 mg and 300 mg WELLBUTRIN XL
- AK1BIOVAIL2548 - Food effect study with highest strength WELLBUTRIN XL (300 mg)

The bioanalytical methods were validated and documented appropriately.

The key findings with respect to the Clinical Pharmacology and Biopharmaceutics of WELLBUTRIN XL are as follows:

- Bioequivalence for bupropion metabolites was demonstrated between the highest strength WELLBUTRIN XL tablet (300 mg) and the approved immediate release product WELLBUTRIN given as 100 mg three times daily. It was noted in the minutes of the pre-IND meeting of October 26, 2001 that a single positive well controlled study would be needed if the bioequivalence study did not meet its objectives, and that metabolite pharmacokinetics would be crucial. Although bioequivalence could not be demonstrated for the parent compound (for which C_{min} was outside of the bioequivalence interval of 0.8 to 1.25), consideration should be given to the active metabolites, since they are responsible for more than 90% of the exposure following administration of bupropion. Therefore it is reasonable to suggest that the two products were comparable in exposure.

  It should be noted that although comparable exposure was demonstrated, there are differences in the shapes of the curves for bupropion in the WELLBUTRIN XL formulation compared with immediate release formulation. The clinical relevance of these differences cannot be predicted based on the pharmacokinetics. However, the comparable exposure and the role of the metabolites in the exposure and pharmacologic activity support the approval of the WELLBUTRIN XL formulation. Of note, for WELLBUTRIN SR, although there were also differences in the shapes of the plasma concentration curves compared to WELLBUTRIN IR, a clinical trial demonstrated efficacy of WELLBUTRIN SR in maintaining antidepressant response.

- Dosage strength equivalence was demonstrated between the 150 mg and 300 mg strengths of WELLBUTRIN XL.

- There is no appreciable effect of food on exposure to bupropion or its metabolites when WELLBUTRIN XL (300 mg) is given with a high fat meal.

In addition, recent data in the literature suggest that several SSRIs (sertraline, paroxetine, and fluvoxamine as well as norfluoxetine) and several antiretroviral drugs (ritonavir, efavirenz, and nelfinavir) inhibit the hydroxylation of bupropion *in vitro*. The Office of Clinical Pharmacology and Biopharmaceutics recommends that the label be revised with respect to the potential for CYP2B6-mediated interactions.

The proposed *in vitro* dissolution method is acceptable. The office of clinical Pharmacology and Biopharmaceutics recommends that the specification be changed to the following:

2 hours:
4 hours:
8 hours:
16 hours:

In addition, it should be noted that the Sponsor has not consistently used tablets for each time point in the dissolution profiles. In the future, the Sponsor should adhere to the practice of using for dissolution profiles.

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommends some revisions in the proposed label text. Please refer to Section 5.

The Division of Scientific Investigations (DSI) has been requested to inspect the clinical site and bioanalytical facilities (Biovail Contract Research, Toronto) of the pivotal BE study, AK1BIOVAIL2543 ("A Two-Way, Crossover, Steady State, Multiple-Dose, Open-Label Fasting Comparative Bioavailability Study of Bupropion HCl 300 mg Extended- Release Tablets (1 x 300 mg Q.D.) vs WELLBUTRIN 100 mg Tablets (TID) in Normal Healthy Non-Smoking Male and Female Subjects). The DSI inspection report is pending.

The OCPB finds that the submitted data in NDA 21-515 is acceptable pending the outcome of the DSI inspection report.

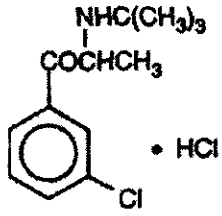
4 Question-Based Review

4.1 General Attributes

4.1.1 What are the highlights of the chemistry and physical-chemical properties of Wellbutrin XL, and the formulation of the drug product?

The following information has been extracted from the proposed labeling.

Wellbutrin XL tablets contain bupropion hydrochloride. Bupropion hydrochloride is chemically designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride and its structural formula is:



The empirical formula of bupropion HCl is $C_{13}H_{18}ClNO \cdot HCl$ and its molecular weight is 276.2. Bupropion HCl is a white crystalline powder that is highly soluble in water.

Wellbutrin XL extended release tablets are diffusion controlled tablets that consist of a tablet core surrounded by coatings that form a membrane responsible for controlling the release of bupropion HCl. Wellbutrin XL tablets are creamy white to pale yellow tablets. According to the sponsor, tablets are printed with edible black ink. The composition of the 150 mg and 300 mg tablets, including inactive ingredients, are shown in the table below.

Composition of WELLBUTRIN XL Tablets, 150 mg and 300 mg, as provided by Sponsor.

Component	150 mg Quantity (mg)	300 mg Quantity (mg)	Function	Reference to Standard
Bupropion Hydrochloride	150.0	300.0	Active Pharmaceutical Ingredient	Biovail
Polyvinyl Alcohol				USP
Glyceryl Behenate				NF
Ethylcellulose				NF
Povidone				USP
Polyethylene Glycol				NF
Methacrylic Acid Copolymer Dispersion				NF
Silicon Dioxide				NF
Triethyl Citrate				NF
Purified Water				USP
Black Ink				Biovail
Total unit dose				

Note:

4.1.2 What is the proposed mechanism of drug action and what is the proposed therapeutic indication?

Bupropion is an antidepressant of the aminoketone class. Its mechanism of action is unknown but is thought to be mediated by noradrenergic and/or dopaminergic mechanisms. According to the sponsor it inhibits neuronal reuptake of norepinephrine and dopamine and does not inhibit monoamine oxidase. The proposed indication is for the treatment of major depressive disorder.

4.1.3 What is the proposed dosage and route of administration?

The proposed adult target dose for WELLBUTRIN XL Tablets is 300 mg/day, given orally once daily in the morning. It is recommended that dosing begin at 150 mg/day as a single daily dose in the morning. If this dose is adequately tolerated, an increase to 300 mg/day may be made as early as day 4 of dosing. An increase in dose to the maximum of 450 mg/day may be considered in patients with no clinical improvement after several weeks of treatment at 300 mg/day.

4.1.4 What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., can disparate efficacy measurements or adverse events reports be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?

The present submission did not include clinical efficacy trials. Exposure-related adverse effects include seizures, with a 10-fold increase in seizure incidence compared to 300 mg per day at doses between 450 and 600 mg per day of the immediate-release formulation of bupropion, according to information provided in the label of WELLBUTRIN SR. The present submission did not evaluate dose-dependence of adverse effects. The studies were conducted in healthy volunteers without clinically significant impairment in factors that could alter exposure-response relationships (such as renal or hepatic impairment, congestive heart failure, age, or concomitant medications).

4.2 General Clinical Pharmacology

4.2.1 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The present submission did not include studies evaluating pharmacodynamic response to WELLBUTRIN XL.

Although the mechanism of action of bupropion as an antidepressant is unknown, it inhibits dopamine uptake and this could be due to occupancy of the dopamine transporter. The present submission included a positron emission tomography (PET) study (OHB10001) to evaluate the relationship between dopamine transporter occupancy and bupropion and metabolites concentration at steady state following administration of bupropion given as 150 mg WELLBUTRIN SR twice daily for 8 days in 6 healthy male volunteers, mean age 30.7 (23-39) years of age. This is a clinically relevant dose. The full study report can be found in the Appendix, Section 6.2.1. PET studies demonstrated approximately 26% occupancy of the dopamine transporter in the striatum up to 24 hours following the last dose of bupropion. Future efforts would be required to characterize the relationship between occupancy and clinical effect, in order to provide a link between dose, pharmacokinetics, and effect as well as to further characterize the mechanism for the effect.

4.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Bupropion and its active metabolites hydroxybupropion, threohydrobupropion, and erthyrohydrobupropion were appropriately identified and measured in the plasma. Please refer to the Bioanalytical Section (4.6). In addition to evaluating the PK of bupropion and its metabolites, the Pharmacological Activity-Weighted Composite (PAWC) of bupropion and its metabolites was determined and evaluated. Bupropion and its metabolites were previously used in approval of WELLBUTRIN SR tablets since approximately 90% of systemic exposure is due

to metabolites, rather than parent drug. It should be noted that the PAWC is a value that is calculated based on relative potency determined in an animal model of antidepressant activity, and does not represent pharmacologic activity in humans.

4.2.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

- *Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship for WELLBUTRIN XL?*

According to the WELLBUTRIN SR label, bupropion and its metabolites display linear kinetics with chronic administration of 300 to 450 mg/day. This relationship was not studied in the present application.

- *Do PK parameters change with time following chronic dosing?*

The pharmacokinetic parameters have not been directly compared following acute and chronic dosing of WELLBUTRIN XL in the same study. The following data summarizes comparable pharmacokinetic data from studies submitted to the present NDA (21-515) for WELLBUTRIN XL after single or multiple doses of 300 mg WELLBUTRIN XL.

	Mean (% CV) Single Dose PK Parameters (Study AK1BIOVAIL2571)	
	t_{max} (h)[a]	$AUC_{0-\infty}$ (ng*h/ml)
Bupropion	5.00 (4.00-8.00)	1728.3 (28)
Bupropion	16.00 (5.50 – 24.00)	1613.6 (39)
Erythyroamino Alcohol		
Bupropion Threoamino Alcohol	8.00 (5.00 – 16.00)	9091.3 (43)
Hydroxybupropion	12.00 (6.00 – 24.00)	23498.8 (41)
PAWC	5.50 (4.50 – 24.00)	70.4 (34)

	Mean (%CV) Multiple Dose PK Parameters (Study AK1BIOVAIL2543)	
	t_{max} (h)[a]	AUC_{0-24} (ng*h/ml)
Bupropion	5.00 (3.00 – 7.00)	1612.0 (30)
Bupropion	8.00 (5.00 – 14.00)	2145.7 (29)
Erythyroamino Alcohol		
Bupropion Threoamino Alcohol	8.00 (5.00 – 14.00)	10987.9 (29)
Hydroxybupropion	7.00 (4.00 – 14.00)	20824.8 (36)
PAWC	6.00 (4.00 – 14.00)	66.5 (27)

[a] median (range)

- *How long is the time to onset and offset of the pharmacological response or clinical endpoint?*

According to the label for WELLBUTRIN SR, 4 weeks may be required before the full antidepressant effect is evident. Efficacy of WELLBUTRIN SR was demonstrated for as long as

44 weeks of maintenance treatment. The offset of the pharmacological response is not described in the summary material provided by the sponsor.

- *Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

A dose-response relationship for bupropion as an antidepressant has not been well-characterized. In comparison with the proposed dosing of WELLBUTRIN XL, the usual adult target dose for WELLBUTRIN SR is 300 mg/day (given as 150 mg twice daily), and doses of 400 mg/day may be considered. The target dose of WELLBUTRIN is also 300 mg/day (given as 100 mg three times daily), with a maximum dose of 450 mg/day in patients who do not have an adequate clinical response.

The once daily dosage regimen for WELLBUTRIN XL is consistent with its extended release profile and long elimination half-life.

4.2.4 What are the basic pharmacokinetic parameters after administration of WELLBUTRIN XL and how does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

According to summary information provided by the sponsor, after administration of bupropion given as immediate release WELLBUTRIN to healthy volunteers the mean apparent oral clearance (Cl/F) was 200 L/hr and the volume of distribution (Vd/F) was 700 L, and the mean elimination half-life was approximately 20 hours. After steady state dosing of this formulation the t_{max} of bupropion was approximately 1.5 hours, while the t_{max} for the active metabolites was approximately 3-4 hours.

In the data submitted for the present NDA, following a single dose of 300 mg WELLBUTRIN XL, the t_{max} for bupropion was approximately 5 hours and the t_{max} for the active metabolites was approximately 8-16 hours (Study AK1BIOVAIL2571). The mean elimination half-life was approximately 22 hours. After steady state dosing of this formulation (300 mg once daily) the t_{max} of bupropion was approximately 5 hours and the t_{max} of the active metabolites was approximately 6-8 hours. After both single and multiple dosing, most of the exposure was from the metabolites as has been previously reported for other formulations, and the mean C_{max} of hydroxybupropion was approximately 7 times higher and the mean AUC_{0-24} was approximately 13 times higher than the respective values of the parent compound. The Metabolite/Parent ratio (metabolite AUC/molecular weight)/(bupropion AUC/molecular weight), with $AUC_{0-\infty}$ for single dose and AUC_{0-24} for multiple dose, as calculated by the sponsor was approximately 13 for hydroxybupropion. More complete information on the pharmacokinetic parameters after single and multiple doses can be found in the tables in Sections 4.5.6 and 4.5.7, respectively.

The pharmacokinetic behavior of WELLBUTRIN XL has not been evaluated in the target population.

It has been previously demonstrated that bupropion is extensively metabolized in humans. According to the labeling for WELLBUTRIN SR, following oral administration of [^{14}C]-

bupropion in humans, 87% of the radioactive dose was recovered in urine and 10% recovered in feces.

4.2.5 What is the inter-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In healthy volunteers, inter-subject variability after administration of single or multiple doses of 300 mg WELLBUTRIN XL in the bioequivalence and dosage strength equivalence studies (2543 and 2571, respectively) was approximately 25-32% for Cmax and 27-30% for AUC for bupropion. For the metabolites the variability was approximately 23-37% for Cmax. For AUC, inter-subject variability was approximately 29% for bupropion erythroamino alcohol and bupropion threoamino alcohol after multiple doses, and approximately 36-53% for hydroxybupropion after multiple doses and for all of the metabolites after single doses. Variability could be due to large interindividual differences in expression of CYP2B6, the P450 isozyme that is involved in the formation of hydroxybupropion, as well as variability in expression of other enzymes involved in metabolism of bupropion that are not thought to be P450 enzymes.

4.3 Intrinsic Factors

4.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

The pharmacokinetics of bupropion have been previously studied in special populations and the influence on exposure can be found in the label for WELLBUTRIN SR (and repeated in the proposed label for WELLBUTRIN XL) as outlined below.

Elderly – A single and multiple dose study has suggested that elderly are at increased risk of exposure to bupropion and its metabolites.

Pediatrics - The immediate release formulation of bupropion has been studied in pediatrics and was well tolerated, but the limited exposure was considered insufficient to assess the safety of bupropion in pediatrics.

Gender – A single dose study did not reveal a sex-related difference in the PK parameters of bupropion.

Race – Evaluation of the effect of race on bupropion pharmacokinetics is not described in the labeling of WELLBUTRIN SR or in the proposed labeling of WELLBUTRIN XL.

Renal Impairment – The effect of renal disease on the pharmacokinetics of bupropion has not been studied, although the elimination of the major metabolites may be affected by reduced renal function.

Hepatic Impairment – The half-life of hydroxybupropion is significantly longer in patients with alcoholic liver disease than in healthy volunteers, and the AUCs for bupropion and

hydroxybupropion were greater in patients with alcoholic liver disease. Cmax and AUC of bupropion and half-lives of bupropion and its metabolites were increased in patients with severe hepatic cirrhosis compared to healthy volunteers.

Genetic Polymorphisms – The role of genetic polymorphisms in the metabolism of bupropion has not been described.

Left Ventricular Dysfunction – No apparent effect on the pharmacokinetics of bupropion or its metabolites was identified in a chronic dosing study in patients with left ventricular dysfunction.

Pregnancy and Lactation – According to the label, there are no adequate and well-controlled studies in pregnant women and the effect on labor and delivery in humans is unknown. Bupropion and its metabolites are secreted in human milk.

4.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied, what dosage regimen adjustments, if any, are recommended for each of these subgroups?

Elderly – The labeling of WELLBUTRIN SR has a precaution stating that care should be taken in dose selection in the elderly due to a likelihood of decreased renal function. It does not give specific guidelines for dosage adjustment other than suggesting a consideration of reduced frequency and/or dose in renal impairment. This recommendation is extended to the proposed labeling of WELLBUTRIN XL.

Pediatrics - The proposed labeling states that safety and effectiveness of WELLBUTRIN XL in pediatric patients below 18 years old have not been established. The Sponsor has submitted a formal request for a partial deferral to conduct a study to fulfill the requirements of the pediatric Rule in children and adolescents ages 7 to 17 years, with a proposal to conduct that study after the approval of the present NDA. According to the Sponsor inclusion of children less than 7 years old is not supported by published literature. Therefore, the Sponsor has requested a waiver with respect to studying pediatric age groups less than 7 years of age.

Renal Impairment - Specific guidelines are not given in the WELLBUTRIN SR label other than suggesting a consideration of reduced frequency and/or dose. This recommendation is extended to WELLBUTRIN XL in the proposed label.

Hepatic Impairment – It is recommended that WELLBUTRIN SR be used with extreme caution in patients with severe hepatic cirrhosis. Specific recommendations are that dose should not exceed 100 mg every day or 150 mg every other day in these patients. In patients with hepatic impairment (including mild to moderate hepatic cirrhosis) caution and consideration of reduced frequency and/or dose is recommended. These guidelines are extended to WELLBUTRIN XL, with the dose not exceeding 150 mg every other day in patients with severe hepatic cirrhosis.

Pregnancy and Lactation – The proposed label of WELLBUTRIN XL reflects the labeling for WELLBUTRIN SR. It is recommended that, although teratology studies in rats and rabbits reveal no evidence of harm to the fetus due to bupropion, this drug be used in pregnancy only if clearly needed. GlaxoSmithKline maintains a Bupropion Pregnancy Registry and the number is

provided. Since bupropion and its metabolites are secreted in human milk, and the potential exists for serious adverse reactions in nursing infants, the label states that a decision should be made whether to discontinue nursing or discontinue the drug, depending on the importance of the drug to the mother.

4.4 Extrinsic Factors

4.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

According to the label for WELLBUTRIN SR (and extended to WELLBUTRIN XL) the effects of cigarette smoking on the pharmacokinetics of bupropion have been studied in healthy volunteers. The study found no statistically significant difference in Cmax, half-life, tmax, AUC, or clearance of bupropion or its metabolites between smokers and nonsmokers after a single 150 mg dose of bupropion.

4.4.2 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

Dosage modification based on smoking status is not required.

4.4.3 Drug-Drug Interactions

4.4.3.1 **Is there an *in vitro* basis to suspect *in vivo* drug-drug- interactions with bupropion that are mediated by CYP450?**

According to the label for WELLBUTRIN SR (extended to the proposed labeling for WELLBUTRIN XL), *in vitro* studies suggest that bupropion is primarily metabolized to hydroxybupropion by CYP2B6. In addition, bupropion and hydroxybupropion are inhibitors of CYP2D6 *in vitro*.

The reviewer has identified two publications in the literature evaluating *in vitro* the potential for P450-mediated drug interactions with bupropion. Hesse et al (Drug Metab Disposition 2000; 28:1176-1183) evaluated potential drug interactions with other antidepressants in human liver microsomes and reported a mean IC_{50} value for paroxetine of approximately 1.6 μM. Sertraline, norfluoxetine, and fluvoxamine also inhibited bupropion metabolism with mean IC_{50} values of 3.2, 4.2, and 6.1 μM, respectively. Hesse et al (Drug Metab Disposition 2001; 29:100-2) have also reported inhibition of bupropion hydroxylation in human liver microsomes by nelfinavir, ritonavir, and efavirenz with mean IC_{50} values of 2.5, 2.2, and 5.5 μM respectively.

4.4.3.2 Is bupropion an inducer of CYP enzymes?

According to the label for WELLBUTRIN SR (extended to the proposed labeling for WELLBUTRIN XL), animal data indicate that bupropion may induce drug-metabolizing enzymes in humans. There is no evidence that it induces its own metabolism.

4.4.3.3 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

There is no information available about the role of bupropion as a substrate or inhibitor of P-glycoprotein.

4.4.3.4 Are there other metabolic/transporter pathways that may be important in the pharmacokinetics of bupropion?

There is no information to address this.

4.4.3.5 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The label does not specify co-administration of another drug.

4.4.3.6 What other co-medications are likely to be administered to the target patient population?

Bupropion may be used with other antidepressants such as SSRIs. It could also potentially be used as an antidepressant in patients with concomitant disease such as HIV (includes medications such as ritonavir, efavirenz, and nelfinavir) or cancer (medications include cyclophosphamide, a CYP2B6 substrate and thiotepa, a CYP2B6 inhibitor).

4.4.3.7 Are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

According to the label for WELLBUTRIN SR (extended to the proposed labeling for WELLBUTRIN XL), after concomitant administration of 800 mg cimetidine with bupropion (two 150 mg tablets of WELLBUTRIN SR) in healthy volunteers the pharmacokinetics of bupropion and hydroxybupropion were unaffected, although there were 16% and 32% increases in AUC and Cmax, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion. A dosage adjustment has not been recommended regarding concomitant administration of cimetidine and bupropion.

According to the label for WELLBUTRIN SR (extended to the proposed labeling for WELLBUTRIN XL), the effects of bupropion on desipramine (a CYP2D6 substrate) pharmacokinetics were evaluated in healthy volunteers. An increase of C_{max}, AUC, and $t_{1/2}$ of desipramine of 2-, 5-, and 2-fold, respectively was observed. The label suggests that co-administration of bupropion with drugs that are metabolized by CYP2D6 should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication, and that if bupropion is added to a regimen containing a substrate of CYP2D6, the need to decrease the dose of the original medication should be considered.

4.4.3.8 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Bupropion is associated with a dose-related risk of seizures, and this risk may be increased if given with other medications that lower the seizure threshold.

Other potential pharmacodynamic drug interactions are listed in the label and include a contraindication for use with MAO inhibitors due to potential for enhanced toxicity of bupropion, caution with levodopa or amantadine administration due to higher incidence of adverse effects, precautions regarding the potential for hypertension in patients receiving nicotine transdermal systems, and adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during treatment with bupropion.

4.4.3.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

In light of the *in vitro* studies suggesting inhibition of bupropion metabolism by SSRIs and antiretroviral drugs, this should be addressed in the label and potentially addressed with a literature search and, if necessary, followed by a drug interaction study *in vivo*. Thiotepa has also been demonstrated *in vitro* to be a substrate and inhibitor of CYP2B6, and this information should be added to the label.

4.4.4 What issues related to dose, dosing regimen, or administration are unresolved, and represent significant omissions?

If a significant increase in exposure were observed following inhibitors of CYP2B6, a determination of the need for dosage adjustment would be required.

Currently the potential for CYP2B6-mediated interactions is addressed in the Clinical Pharmacology section of the label with a focus on interaction with agents that are metabolized by CYP2B6. The Drug Interactions section of the label states that the potential exists for a drug interaction with drugs that affect the CYP2B6 isoenzyme, and lists only orphenadrine and cyclophosphamide as examples.

4.5 General Biopharmaceutics

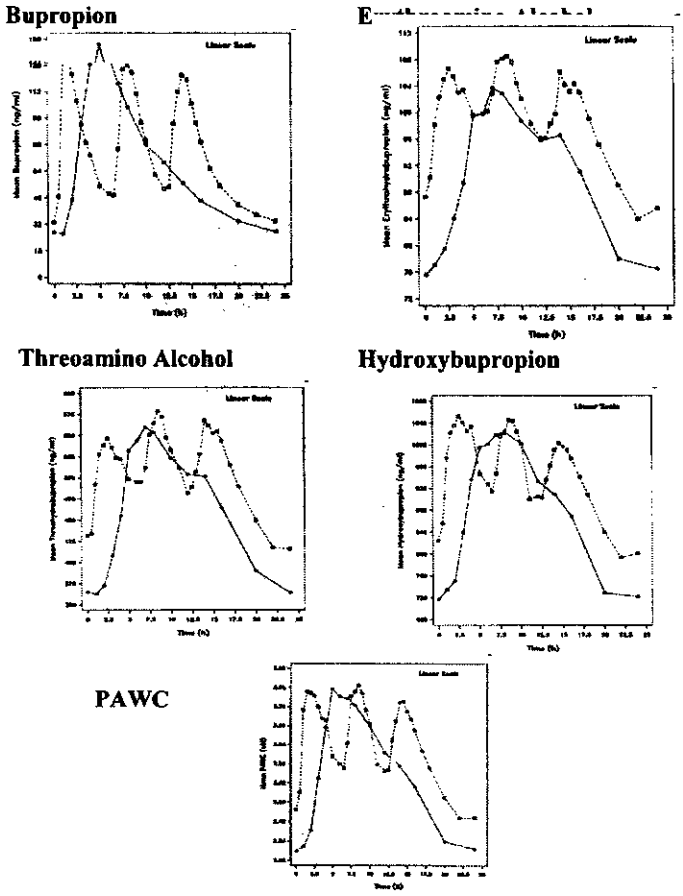
4.5.1 If the NDA is for a modified release formulation of an approved immediate product without supportive safety/efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

- *What is the bioavailability of WELLBUTIN XL 300 mg relative to immediate release WELLBUTRIN tablets (100 mg three times daily)?*

Study AK1BIOVAIL2543 assessed the relative oral bioavailability of a once daily 300 mg WELLBUTRIN XL tablet (test) compared to the reference WELLBUTRIN immediate release tablets given 100 mg three times daily (tid) under steady-state fasting conditions. The full study review can be found in the Appendix, Section 6.2.4. This was a randomized, 2-period, 2-

treatment, 2-sequence crossover multiple dose steady state study. The study was completed in 30 healthy subjects (22 M/8 F; mean age 34 (20-50) years of age).

The plasma concentration time course and pertinent pharmacokinetic parameters for bupropion, its metabolites, and the PAWC are shown in the Figures and Table below.



Mean Steady State Plasma Concentration Time Course for Bupropion and Its Metabolites After Administration of Test (solid circles) or Reference (open squares) Formulations in Study 2543 (as Provided by Sponsor)

Steady State pharmacokinetic parameters (arithmetic mean) for bupropion and metabolites

	Test (Bupropion XL) (% CV) n=30	Reference (Wellbutrin) (% CV) n=30
Bupropion		
t_{max} (h)[a]	5.00 (3.00-7.00)	1.50 (1.00-3.00)
C_{max} (ng/mL)	[redacted] (28)	[redacted] (32)
AUC $_{0-24}$ (ng*h/mL)	1612.0 (30)	1792.0 (27)
Cmin (ng/ml)	27.6 (39)	34.1 (37)
Cav (ng/ml)	67.2 (30)	74.7 (27)
Degree of Fluctuation (%)	212.6 (19)	190.0 (21)
Swing (%)	554.6 (35)	439.6 (32)
Bupropion Erythroamino Alcohol		
t_{max} (h)[a]	8.00 (5.00-14.00)	2.50 (1.07-3.50)
C_{max} (ng/mL)	[redacted] (27)	[redacted] (22)
AUC $_{0-24}$ (ng*h/mL)	2145.7 (29)	2353.7 (27)
Cmin (ng/ml)	76.5 (34)	85.6 (31)
Cav (ng/ml)	89.4 (29)	98.1 (27)
Degree of Fluctuation (%)	38.1 (40)	38.9 (87)
Swing (%)[b]	46.0 (35)	46.2 (94.7)
Bupropion Threoamino Alcohol		
t_{max} (h)[a]	8.00 (5.00-14.00)	2.50 (1.07-5.00)
C_{max} (ng/mL)	[redacted] (27)	[redacted] (22)
AUC $_{0-24}$ (ng*h/mL)	10987.9 (29)	12051.4 (26)
Cmin (ng/ml)	364.4 (34)	415.7 (29)
Cav (ng/ml)	457.8 (29)	502.1 (26)
Degree of Fluctuation (%)	50.5 (34)	45.2 (48)
Swing (%)[b]	65.7 (40)	56.3 (52)
Hydroxybupropion		
t_{max} (h)[a]	7.00 (4.00-14.00)	2.50 (1.00-4.00)
C_{max} (ng/mL)	[redacted] (35)	[redacted] (29)
AUC $_{0-24}$ (ng*h/mL)	20824.8 (36)	22456.1 (31)
Cmin (ng/ml)	722.2 (39)	800.9 (33)
Cav (ng/ml)	867.7 (36)	935.7 (31)
Degree of Fluctuation (%)	44.3 (37)	40.8 (77)
Swing (%)[b]	54.6 (41)	49.2 (83)
PAWC		
t_{max} (h)[a]	6.00 (4.00-14.00)	2.00 (1.00-3.00)
C_{max} (µM)	[redacted](25)	[redacted](22)
AUC $_{0-24}$ (µM*h)	66.5 (27)	72.1 (23)
Cmin (µM)	2.2 (32)	2.4 (26)
Cav (µM)	2.8 (27)	3.0 (23)
Degree of Fluctuation (%)	57.7 (21)	50.1 (36)
Swing (%)[b]	75.2 (35)	62.9 (39)

[a] median (range)
[b] calculated by reviewer

No evidence of dose-dumping was observed after administration of WELLBUTRIN XL.

The 90% confidence intervals on the geometric means of the C_{max}, C_{min}, and AUC_{0-24} ratios are within the bioequivalence interval of 0.8 to 1.25 for bupropion, its metabolites, and the PAWC, with the exception of bupropion C_{min}. Bupropion C_{min} was approximately 19% lower for WELLBUTRIN XL than the Reference formulation, and the ratio of geometric means was 0.8

with a 90% confidence interval of 0.76 to 0.85. Since the majority of the exposure is due to the metabolites, and bioequivalence is demonstrated with the metabolites, and for all other parameters including C_{max} and AUC for bupropion, the two formulations can be considered to be comparable *in vivo*. As previously noted the PAWC is a value that is calculated based on relative potency determined in an animal model of antidepressant activity, and does not represent pharmacologic activity in humans.

Of note, WELLBUTRIN SR 150 mg tablets were approved based on BE results for the parent and 3 metabolites (NDA 20-358). BE criteria in that case were met except for Cmax for the parent compound (90% CI was [redacted]

- *What dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?*

The once daily 300 mg WELLBUTRIN XL demonstrated comparable exposure to the immediate release product given as 100 mg three times daily as discussed above. Therefore, dosage regimen changes are not necessary.

It should be noted that although comparable exposure was demonstrated, there are differences in the shapes of the curves for bupropion in the WELLBUTRIN XL formulation compared with immediate release formulation. The clinical relevance of these differences cannot be predicted based on the pharmacokinetics. However, the comparable exposure and the role of the metabolites in the exposure and pharmacologic activity support the approval of the WELLBUTRIN XL formulation. Of note, for WELLBUTRIN SR, although there were also differences in the shapes of the plasma concentration curves compared to WELLBUTRIN IR, a clinical trial demonstrated efficacy of WELLBUTRIN SR in maintaining antidepressant response.

4.5.2 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

BCS-based waivers do not apply in the case of an extended release product.

4.5.3 What is the in vivo relationship of the proposed to be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

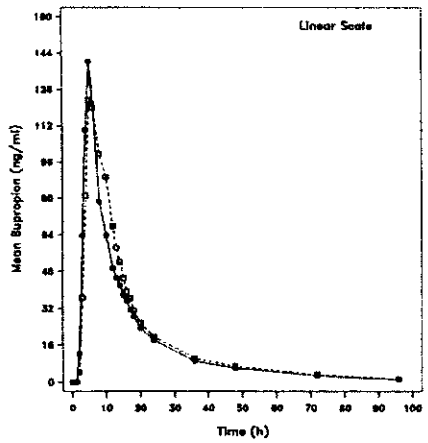
This NDA did not include a pivotal clinical trial. The proposed to-be-marketed formulation is the same formulation that was used in the bioequivalence studies except that the bioequivalence study dosage strengths were not imprinted. The imprinted tablets should meet the selected dissolution specifications. This has been referred to the Chemistry reviewer.

4.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

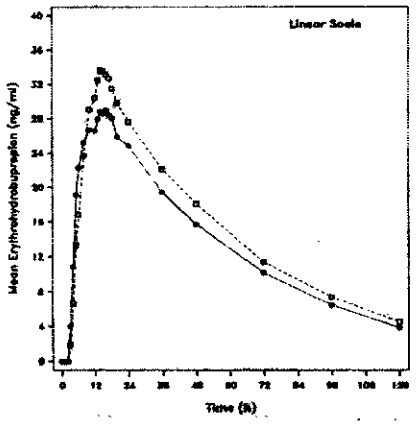
A food effect study (AK1BIOAVAIL2548) evaluated the effect of food (a high fat meal) on the oral bioavailability of bupropion after administration of WELLBUTRIN XL 300 mg relative to

administration in the fasting state. The dosage strength used is the highest proposed dosage strength of this product. The full study review can be found in the Appendix, Section 6.2.2. This was a single dose, randomized, 2- period, 2-treatment, 2-sequence crossover study. The study was completed in 31 healthy subjects (23 M/8 F; mean age 31.8 (21-46) years of age). The plasma concentration time course and pertinent pharmacokinetic parameters are shown in the Figures and Table below.

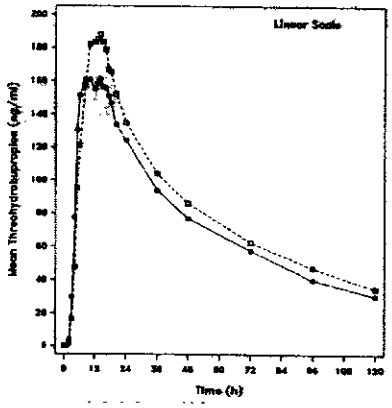
Bupropion



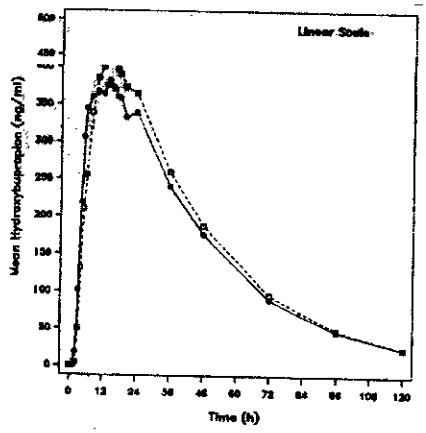
Erythroamino Alcohol



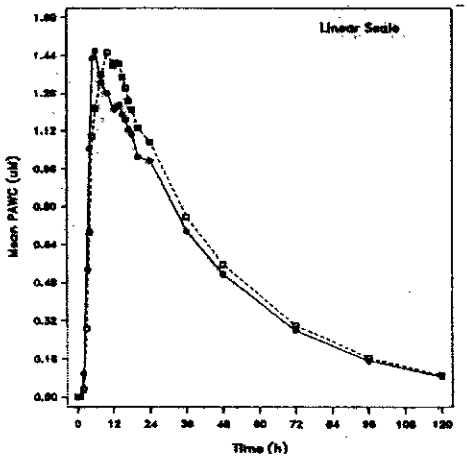
Threoamino Alcohol



Hydroxybupropion



PAWC



Mean Plasma Concentration Time Course for Bupropion and its Metabolites and the PAWC after Administration of Bupropion XL During the Test (open squares) and Reference (solid circles) Periods in Study AK1BIOVAIL2548 (as provided by Sponsor).

Pharmacokinetic parameters (arithmetic mean) for bupropion and metabolites (Study 2548)

	Test (Fed) (% CV) n=31	Reference (Fasting) (% CV) n=31
Bupropion		
t_{max} (h)[a]	5.07 (4.00-12.00)	5.00 (4.00 – 8.00)
C_{max} (ng/mL)	[redacted] (31)	[redacted] (32)
AUC $_{0-t}$ (ng*h/mL)	1775.4 (30)	1628.4 (31)
AUC $_{0-\infty}$ (ng*h/mL)	1832.5 (30)	1678.4 (31)
$t_{1/2}$ (hr)	21.8 (27)	21.2 (29)
λ_z (hr^{-1})	0.0347 (32)	0.0359 (34)
Bupropion Erythroamino Alcohol		
t_{max} (h)[a]	14.00 (8.00 – 24.02)	15.00 (5.00 – 24.00)
C_{max} (ng/mL)	[redacted] (26)	[redacted] (32)
AUC $_{0-t}$ (ng*h/mL)	1803 (38)	1634.6 (45)
AUC $_{0-\infty}$ (ng*h/mL)	2116.0 (48)	1867.7 (52)
$t_{1/2}$ (hr)	35.2 (34)	33.9 (33)
λ_z (hr^{-1})	0.0215 (27)	0.0223 (28)
Bupropion Threoamino Alcohol		
t_{max} (h)[a]	8.00 (4.00 – 24.00)	13.00 (6.00 – 18.00)
C_{max} (ng/mL)	[redacted] (47)	[redacted] (55)
AUC $_{0-t}$ (ng*h/mL)	9769.7 (63)	9032.2 (73)
AUC $_{0-\infty}$ (ng*h/mL)	13280.6 (71)	11696.3 (77)
$t_{1/2}$ (hr)	55.2 (32)	55.2 (38)
λ_z (hr^{-1})	0.0139 (30)	0.0139 (32)
Hydroxybupropion		
t_{max} (h)[a]	14.00 (8.00 – 24.02)	14.00 (5.00 - 24.00)
C_{max} (ng/mL)	[redacted] (40)	[redacted] (38)
AUC $_{0-t}$ (ng*h/mL)	19733.5 (48)	18939.8 (44)
AUC $_{0-\infty}$ (ng*h/mL)	20886.1 (49)	19852.7 (46)
$t_{1/2}$ (hr)	24.1 (22)	24.0 (20)
λ_z (hr^{-1})	0.0301 (22)	0.0302 (23)
PAWC		
t_{max} (h)[a]	10.00 (5.00 – 17.00)	6.00 (4.00 – 14.00)
C_{max} (µM)	[redacted] (33)	[redacted] (27)
AUC $_{0-t}$ (µM*h)	63.3 (42)	60.1 (40)
AUC $_{0-\infty}$ (µM*h)	68.0 (43)	63.8 (41)
$t_{1/2}$ (hr)	27.6 (22)	27.2 (26)
λ_z (hr^{-1})	0.0263 (22)	0.0271 (24)

[a] median (range)

No evidence of dose dumping after administration with food was observed, with C_{max} for bupropion in both periods occurring at approximately 5 hours, in agreement with t_{max} observed in the previous single dose and multiple dose studies of WELLBUTRIN XL (AK1BIOVAIL2751 and AK1BIOVAIL2543).

The 90% confidence intervals on the geometric means of the C_{max} and AUC ratios are within the bioequivalence interval of 0.8 to 1.25 for bupropion and for the predominant metabolite hydroxybupropion. They are outside of the bioequivalence interval for the Cmax and AUC $_{0-\infty}$ for bupropion erythroamino ([redacted] and (1.05, 1.27), respectively, and the AUC $_{0-t}$ for bupropion threoamino alcohol (1.04, 1.26). This was due to an approximate [redacted] and 13% increase in bupropion erythroamino Cmax and $AUC_{0-\infty}$, respectively and an approximate 8% increase in bupropion threoamino AUC $_{0-t}$.

Although the 90% Confidence interval is not contained in the equivalence limits of 80%-125% for 2 of the metabolites of bupropion, the differences between the fed and fasting states are very small (≤ 15%). Therefore, this study demonstrates that there is no appreciable effect of food on exposure to bupropion or its metabolites when bupropion extended release tablets (300 mg) are given with a high fat meal.

- *What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

The sponsor can claim that no food effect on bioavailability is expected, and could state that WELLBUTRIN XL may be taken without regard to meals.

4.5.5 When would a fed BE study be appropriate and was one conducted?

A fed BE study is not necessary in this case.

4.5.6 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

Dissolution method development is reviewed in the Appendix, Section 6.2.6. *In vitro* dissolution specifications were based on lots from the proposed commercial formulation that were used in the pharmacokinetic studies AK1BIOVAIL 2543, 2548, and 2571. The sponsor has proposed the following dissolution method and specifications:

Apparatus:	USP Apparatus 1 (Basket)
Medium:	0.1 N HCl
Volume:	900 ml
Rotation Speed:	75 rpm
Specification:	2 hours:
	4 hours: [redacted]
	8 hours:
	16 hours:

The Office of Clinical Pharmacology and Biopharmaceutics finds the proposed dissolution method acceptable. We recommend that the specification be changed as follows:

2 hours:
4 hours:
8 hours:
16 hours:

In addition, it should be noted that the Sponsor has not consistently used tablets for each time point in the dissolution profiles. In the future, the Sponsor should adhere to the practice of using for dissolution profiles.

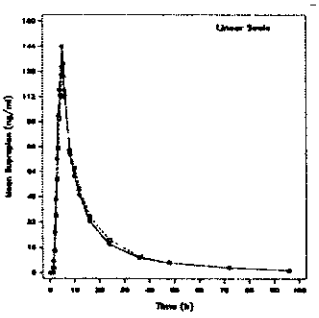
4.5.7 Are different-strength formulations bioequivalent based on standard criteria? What clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Clinical efficacy trials were not conducted for this NDA.

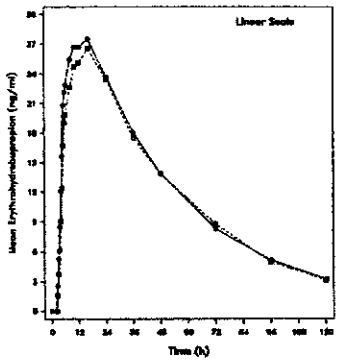
- *Are the 150 mg and 300 mg dosage strengths of WELLBUTIN XL bioequivalent?*

Dosage strength equivalence of the 150 mg and 300 mg dosage strengths of WELLBUTRIN XL was evaluated in healthy volunteers in Study AK1BIOVAIL2571. The full study review can be found in the Appendix, Section 6.2.3. This was a single dose, randomized, 2-period, 2-treatment, 2-sequence crossover study. The study was completed in 35 subjects (19 M/16 F; mean age 34.3 years (19-55). The plasma concentration time course and pertinent pharmacokinetic parameters are shown in the Figures and Table below.

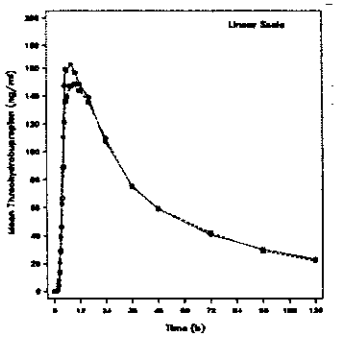
Bupropion



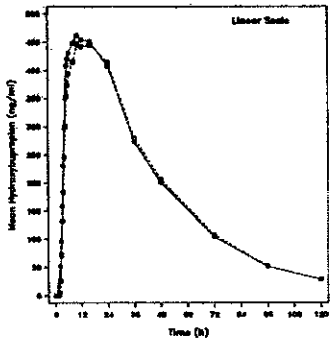
Erythroamino Alcohol



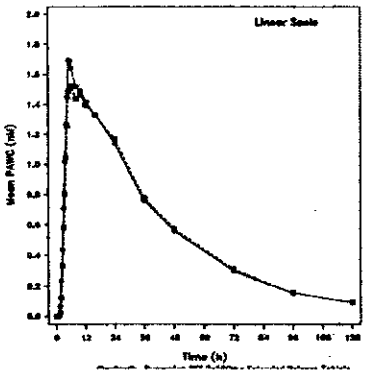
Threoamino Alcohol



Hydroxybupropion



PAWC



Mean Plasma Concentration Time Course for Bupropion and its Metabolites and the PAWC After Administration of WELLBUTRIN XL Tablets During the Reference (300 mg tablet, open squares) or Test (2x 150 mg tablet, solid circles) Periods in Study AK1BIOVAIL2571.

Pharmacokinetic parameters (arithmetic mean) for bupropion and metabolites (Study 2571)

	Test (2x 150 mg tablets) (% CV) n=35	**Reference (300 mg tablet)** (% CV) n=35
Bupropion		
t_{max} (h)[a]	5.00 (3.5 - 8.00)	5.00 (4.00 - 8.00)
C_{max} (ng/mL)	[redacted] (25)	[redacted] (32)
AUC $_{0-t}$ (ng*h/mL)	1648.9 (29)	1676.6 (28)
AUC $_{0-\infty}$ (ng*h/mL)	1702.7 (29)	1728.3 (28)
$t_{1/2}$ (hr)	22.7 (33)	21.8 (34)
λ_z (hr^{-1})	0.0355 (49)	0.0373 (49)
Bupropion Erythroamino Alcohol		
t_{max} (h)[a]	16.00 (6.00 - 16.15)	16.00 (5.50 - 24.00)
C_{max} (ng/mL)	[redacted] (23)	[redacted] (24)
AUC $_{0-t}$ (ng*h/mL)	1508.8 (40)	1441.8 (34)
AUC $_{0-\infty}$ (ng*h/mL)	1702.7 (46)	1613.6 (39)
$t_{1/2}$ (hr)	32.2 (27)	32.1 (29)
λ_z (hr^{-1})	0.0232 (29)	0.0232 (26)
Bupropion Threoamino Alcohol		
t_{max} (h)[a]	8.00 (5.00 - 16.00)	8.00 (5.00 - 16.00)
C_{max} (ng/mL)	[redacted] (35)	[redacted] (36)
AUC $_{0-t}$ (ng*h/mL)	7548.1 (48)	7262.9 (42)
AUC $_{0-\infty}$ (ng*h/mL)	9428.7 (53)	9091.3 (43)
$t_{1/2}$ (hr)	50.5 (33)	51.5 (33)
λ_z (hr^{-1})	0.0150 (31)	0.0149 (33)
Hydroxybupropion		
t_{max} (h)[a]	10.00 (5.00 - 24.17)	12.00 (6.00 - 24.00)
C_{max} (ng/mL)	[redacted] (37)	[redacted] (36)
AUC $_{0-t}$ (ng*h/mL)	22506.3 (42)	22380.3 (39)
AUC $_{0-\infty}$ (ng*h/mL)	23634.2 (44)	23498.8 (41)
$t_{1/2}$ (hr)	24.0 (20)	24.1 (19)
λ_z (hr^{-1})	0.0301 (23)	0.0298 (19)
PAWC		
t_{max} (h)[a]	5.50 (4.00 - 12.00)	5.50 (4.50 - 24.00)
C_{max} (µM)	[redacted] (24)	[redacted] (27)
AUC $_{0-t}$ (µM*h)	67.3 (35)	66.8 (33)
AUC $_{0-\infty}$ (µM*h)	71.0 (37)	70.4 (34)
$t_{1/2}$ (hr)	25.9 (20)	25.9 (19)
λ_z (hr^{-1})	0.0281 (24)	0.0278 (21)

[a] median (range)

The 90% confidence intervals on the geometric means of the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ ratios are within the bioequivalence interval of 0.80 to 1.25. Therefore, the two dosage strengths are considered bioequivalent.

- *Can the 150 and 300 mg strength tablets be combined to achieve the maximum recommended daily dose of 450 mg?*

It has previously been demonstrated that the pharmacokinetics of bupropion and its metabolites are linear following chronic administration of 300 to 450 mg/day. The present NDA has demonstrated dosage strength equivalence of the 150 mg and 300 mg tablets. Therefore, the 150 mg and 300 mg tablets can be combined to achieve the maximum recommended dose of 450 mg daily.

4.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

The only product used was the already approved WELLBUTRIN immediate release tablet.

4.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

A DSI inspection of study AK1BIOVAIL2543, the pivotal BE study, has been requested and the results are pending.

4.5.10 If replicate design studies were conducted and individual BE was analyzed, what were the outcomes with respect to variability and subject-by-formulation interactions?

These studies were not conducted for WELLBUTRIN XL.

4.6 Bioanalytical Method

4.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

A liquid chromatography [redacted] mass spectrometry (LC-MS/MS) assay was used for analysis of bupropion and its metabolites bupropion erythroamino alcohol, bupropion threoamino alcohol, and hydroxybupropion in human plasma. A detailed description of the method is found in the Appendix, Section 6.2.5.

4.6.2 Which metabolites have been selected for analysis and why?

Bupropion as well as its metabolites bupropion erythroamino alcohol, bupropion threoamino alcohol, and hydroxybupropion have been selected for analysis. These are active metabolites, and in animal models that screen for antidepressant activity show potencies after intraperitoneal injection that are 0.2, 0.2, 0.6 times that of bupropion, respectively, according to information provided by the Sponsor. Although the relative potencies are lower than that of bupropion, the

plasma concentrations are higher, and the metabolites account for approximately 90% of the exposure following administration of bupropion.

4.6.3 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

For all moieties measured, the total is measured. According to the label for WELLBUTRIN SR, bupropion is 84% bound to human plasma proteins at concentrations up to 200 µg/ml, with similar protein binding for hydroxybupropion. The extent of protein binding of threoamino alcohol is half that seen with bupropion. Since previous evaluations of bupropion and its metabolites have measured total levels, it is acceptable to continue to measure total concentrations, allowing for inter-study comparisons.

4.6.4 What bioanalytical methods are used to assess concentrations?

- *What is the range of the standard curve and how does it relate to the requirements for the clinical studies?*

Linearity was established in the range of [redacted] for bupropion, erythroamino alcohol, threoamino alcohol, and hydroxybupropion, respectively in the method used for the BE studies reviewed for the present NDA. The endpoints of these ranges (the LLOQ and ULOQ) bracket the range of plasma concentrations observed in the pharmacokinetic studies that were evaluated.

- *Is the bioanalytical method adequately documented and validated?*

The bioanalytical method is adequately documented and validated, and the performance of the assays for the clinical pharmacology studies is considered acceptable.

31 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

6.2 Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

6.2.1 PET STUDY OF DOPAMINE TRANSPORTER OCCUPANCY

AN OPEN LABEL POSITRON EMISSION TOMOGRAPHY STUDY TO EVALUATE DOPAMINE TRANSPORTER OCCUPANCY, AS MEASURED BY ^{11}C-βCIT-FE FOLLOWING 150 MG WELLBUTRIN SR TWICE DAILY FOR 8 DAYS IN HEALTHY MALE VOLUNTEERS

Study Investigators and Site:

[redacted]

Protocol Number: OHB10001

OBJECTIVES:

To define the relationship between dopamine transporter occupancy and bupropion (and metabolites(s)) concentration at steady state.

To determine the time course of occupancy of bupropion (and metabolites(s)) at the DA transporter using ^{11}C-βCIT-FE at steady-state over 12 and 24 hours.

FORMULATIONS:

The product used in OHB10001 was WELLBUTRIN SR 150 mg tablets (GlaxoSmithKline, Inc.).

STUDY DESIGN:

This study was a multiple dose, 1 treatment, open-label study. Inclusion criteria included healthy nonsmoking males, 18 to 55 years of age. Exclusion criteria included previous participation in a PET study, use of any prescription medication within four weeks of the Treatment Phase, ingestion of alcohol or caffeine-containing food or beverage within 72 hours prior to the first dose of study medication and throughout the treatment period, and ingestion of OTC medications including vitamins and antacids within 72 hours before the first dose of study medication and continuing through study completion.

Between 1 and 7 days prior to initial bupropion dosing, a baseline PET study was performed with 300 MBq of ^{11}C-labeled N-omega-fluoroalkyl-2 beta-carboxy-3-beta-(4-iodophenyl) nortropane ester (^{11}C-βCIT-FE). According to the Sponsor, ^{11}C-βCIT-FE is widely used as a selective ligand for the dopamine transporter, and had previously been shown to be displaced from the dopamine transporter by bupropion in a dose-dependent fashion and was therefore

acceptable as a PET ligand. Following the baseline PET study, each subject received a single oral dose of 150 mg sustained-release bupropion HCl administered every 24 hours in the morning for 3 consecutive days (Days 1-3) followed by 7-1/2 days of 150 mg sustained-release bupropion HCl given every 12 hours (Days 4-10). Subject reported to the outpatient clinic for pre-dose blood sampling for pharmacokinetic (PK) analysis on the mornings of Days 8-10. Subjects were admitted to the study unit on the evening of Day 10 and remained there until the morning of Day 12. On the morning of Day 11, following a fast of at least 8 hours, each subject receiving 150 mg sustained-release bupropion HCl (12 hours following the previous evening dose). Blood sampling was performed at fixed times following the morning dose on Day 11. At 3, 12, and 24 hours following the dose on Day 11, subjects were injected with the PET tracer ^{11}C-βCIT-FE and scanning was conducted.

Blood samples were collected at fixed times. Samples were collected on Day 8-10 just prior to the morning dose. On Day 11, samples were collected at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 12.75, 13.5, and 24, 24.75, and 25.5 hours post-drug administration. Details of the storage conditions were not described.

A single blood sample was also collected for pharmacogenetic assessments that included NET and DAT transporters, CYP2B6, and UDP glucuronosyl transferases.

ASSAY:

Details of the analytical methods and assay performance were not provided. According to the Sponsor, samples were analyzed for bupropion, hydroxybupropion and composite of erythrohydrobupropion and threohydrobupropion using a validated LC/MS/MS assay. The lower limit of quantification was [redacted] for bupropion, [redacted] for hydroxybupropion and [redacted] for erythro/threohydrobupropion. Samples were also analyzed for the hydroxybupropion enantiomers, [redacted] (the (+)-enantiomer) and [redacted] using a non-GLP LC/MSMS assay for which the lower limit of quantitation was [redacted]

RESULTS:

Demographics

Six male Caucasian subjects were enrolled and completed the study. The mean age was 30.7 and the age range was 23-39 years of age. The (mean ± SD) was 80.0 ± 14.5 kg.

Pharmacokinetics

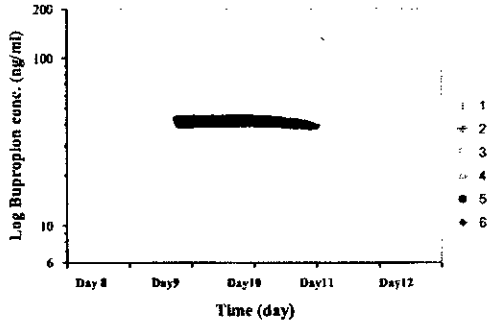
Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters, as provided by Sponsor, are shown in Table 2 below.

Table 2. Pharmacokinetic parameters for bupropion and metabolites at steady state

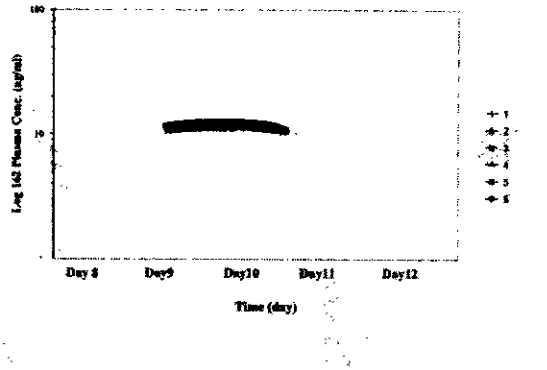
	Bupropion Mean (% CV)	**Hydroxybupropion** Mean (% CV)	[redacted] Mean (% CV)	Mean (% CV)	**Threo+ Erythro** Mean (% CV)
t_{max} (h)[a]	1.50 (1.00-1.50)	3.75 (2.00-5.00)			2.50 (0.50-4.00)
C_{max} (ng/mL)		[redacted] (31)			[redacted] (31)
C_{min} (ng/mL)	105.8 (19)	397.7 (38)			398.0 (172.8)
AUC $_{0-\tau}$ (ng*h/mL)	36.7 (25)	5350.7 (34)			5540.2 (38)
AUC $_{0-t}$ (ng*h/mL)	752.4 (21)	9675.4 (38)			10501 (40)
$t_{1/2}$ (hr)	1088.6 (23)	23.8 (27)			42.3 (18)
λ_z (hr^{-1})	11.0 (11)	0.031 (27)			0.017 (17)
	0.064 (25)				

[a] median (range)
NR (not reported)

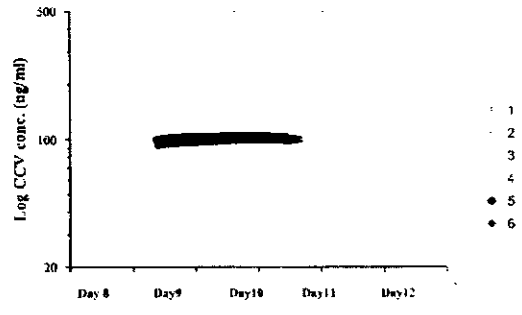
Individual plasma concentrations for bupropion and for the composite concentration value (CCV) reflecting a combination of bupropion, [redacted] and erythro/threohydrobupropion are shown in the figures below.



Individual plasma concentrations vs. time of bupropion following PO administration of WELLBUTRIN SR (150 mg Q12h) in 6 healthy volunteers.



Individual plasma concentrations vs. time of [redacted] following PO administration of WELLBUTRIN SR (150 mg Q12h) in 6 healthy volunteers.

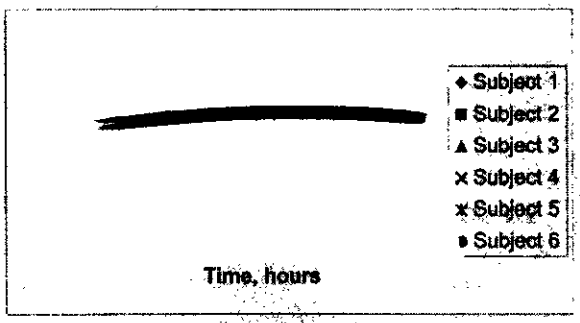


Individual plasma CCV vs. time following PO administration of WELLBUTRIN SR (150 mg Q12h) in 6 healthy volunteers.

Pharmacodynamics

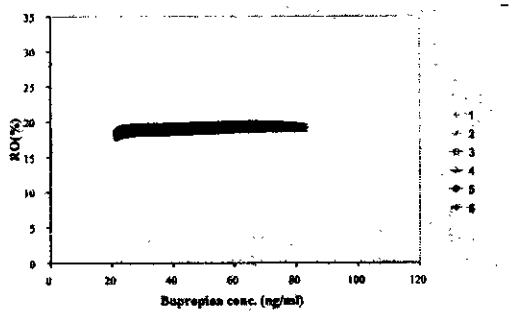
The PET studies evaluated specific binding of ^{11}C-CIT-FE in the striatum after administration of bupropion. The mean dopamine transporter occupancy remained at approximately 26% at the 3 hour, 12 hour, and 24 hour time points after the last dose of bupropion, as shown in the figure below (provided by Sponsor).

Figure 5: The dopamine transporter occupancy (RO, %) in the striatum at T=3, 12 and 24 hours[4] after the last dosing of WELLBUTRIN SR for subjects 1-6

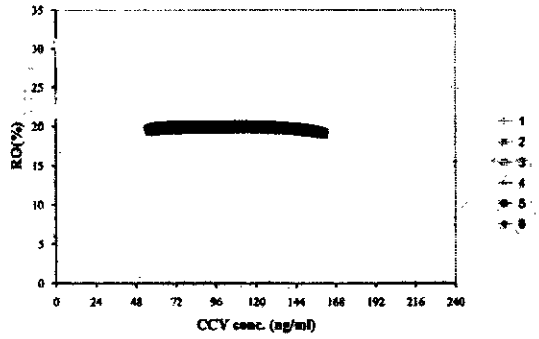


[4] 3, 10 and 22 hours after the last dosing for subject 6.

The comparison between occupancy and plasma concentrations of bupropion or the CCV, shown below, demonstrate that although the plasma concentrations change over the 24 hour period, the occupancy remains relatively constant.



re 5 Day 11, individual bupropion concentrations collected at 3, 12 and 24 hours after bupropion administration vs. RO% evaluated at the same times



re 6 Day 11, individual CCV measured at 3, 12 and 24 hours after bupropion administration vs. RO% evaluated at the same times

Pharmacogenetics

According to the Sponsor, no apparent relationships were observed between DAT and NET variants and dopamine transporter occupancy, and no apparent relationships were observed between bupropion and hydroxybupropion exposure and variants in the [redacted] genes. The Sponsor notes that the conclusions are limited by the small number of subjects in the study.

Safety

According to the Sponsor, four of six subjects experienced at least one adverse event, and all adverse events were considered mild to moderate. Adverse events considered related to study drug included dizziness, somnolence, headache, and vomiting.

CONCLUSIONS:

PET studies with ^{11}C-CIT-FE demonstrated approximately 26% occupancy of the dopamine transporter in the striatum up to 24 hours following the last dose of bupropion given as WELLBUTRIN SR, 150 mg every 12 hours, that is a clinically relevant dose. Future efforts would be required to evaluate the effects on the noradrenaline transporter, and to characterize the relationship between occupancy and clinical effect, in order to provide a link between dose, pharmacokinetics, and effect as well as to further characterize the mechanism for the effect.

6.2.2 FOOD-EFFECT STUDY

A TWO-WAY, CROSSOVER, OPEN-LABEL, SINGLE DOSE, FOOD-EFFECT, COMPARATIVE BIOAVAILABILITY STUDY OF BUPROPION HCL EXTENDED RELEASE 300 MG TABLETS IN NORMAL HEALTHY NON-SMOKING MALE AND FEMALE SUBJECTS

Study Investigators and Site:
Paul Y. Tam, MD, FRCP, FACP
Biovail Contract Research
Toronto, Ontario, Canada

Protocol Number: AK1BIOVAIL2548

OBJECTIVES:

To evaluate the effect of food on the rate and extent of absorption of a once daily formulation of bupropion hydrochloride (HCl) extended release tablets (300 mg) under single-dose conditions.

FORMULATIONS:

Table 1. Product used in AK1BIOVAIL2548

	Package Lot Number	Dose Form Lot Number	Manufacture Date (Dates of Study)
Bupropion HCl 300 mg extended release tablets (Biovail Corporation, USA)	01K211	01L088	October 2001 (January 26, 2002 – February 15, 2002)

Stability studies were ongoing at the time of review. According to the Sponsor, the test product was stable for at least 9 months.

STUDY DESIGN:

This study was a single dose, open-label, randomized, 2-period, 2-treatment, 2-sequence crossover study, as shown in Table 1, below. For Treatment A, subjects received a single dose of bupropion HCl extended release 300 mg tablet with 240 ml of ambient temperature water following an overnight fast of at least 10 hours (treatment period R). Additional water was not allowed from 1 hour pre-dose until 1 hour after dose. Food was not given until more than 4 hours after the dose. For Treatment B, subjects received a single dose of bupropion HCl extended release 300 mg tablet with 240 ml ambient temperature water within 5 minutes following the complete ingestion of a high-fat content breakfast (treatment period T). Additional food was not given until more than 4 hours after the dose. Additional water was not allowed from 1 hour pre-dose until 1 hour after dose. There was a 2- week washout between study periods. The 300 mg dose of the extended release product is the highest proposed dosage strength of this product.

The test meal consisted of the following: one fried egg, one slice of Canadian bacon, one buttered English muffin, one serving of hash brown potatoes, one slice of American cheese, eight ounces of whole milk, and six ounces of orange juice. This meal (790 calories) derived 17% of calories from protein, 34% of calories from carbohydrate, and 49% of calories from fat.

Other meals and beverages were free of grapefruit products, xanthines, and caffeine, and were identical during the study periods.

Table 2. Treatment Sequence in AK1BIOVAIL2548

Sequence Number	Treatment Period 1	Treatment Period 2
1	A (R)	B (T)
2	B (T)	A (R)

Inclusion criteria included healthy nonsmoking males or females, 18 years of age and older. Exclusion criteria included use of prescription medication (including monoamine oxidase inhibitors) within 14 days and over-the-counter medication within 7 days prior to the study. Oral contraceptives or contraceptive implants were not allowed within 30 days and depot injection of a progestogen drug was not allowed within 1 year prior to investigational product administration.

Subjects were asked to abstain from alcohol, grapefruit juice, caffeine, and xanthine-containing foods and fluids from 48 hours prior to the start of the study period until the final blood draw.

Blood samples were collected at fixed times and plasma stored at –70° C until analyzed. Samples were collected at 0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 13.0, 14.0, 15.0, 16.0, 17.0, 18.0, 20.0, 24.0, 36.0, 48.0, 72.0, 96.0, and 120 hours post-drug administration.

ASSAY:

Table 3. Performance of Analytical Method for AK1BIOVAIL2548

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-day CV (%)	Inter-day Accuracy (%)
Bupropion	LC/MS/MS					5.0 5.4* 3.3 6.5	
Bupropion Erythroamino alcohol	LC/MS/MS					6.9 4.7* 3.2 3.6	
Bupropion Threoamino Alcohol	LC/MS/MS					6.2 3.9* 2.7 3.9	
Hydroxybupropion	LC/MS/MS					5.4 5.3* 3.8 6.6	

*Excluding samples that were out of acceptance range; calculated by reviewer.

Two calibration curves and duplicate QC samples (at 4 concentration levels) were analyzed with each batch of study samples. At least 6 out of 8 QC samples were within ± of their respective nominal value, except for 1 run for hydroxybupropion in which 5 out of 8 samples (62.5%) were within ± of the nominal value. Study samples were stored at –70° C. Samples were analyzed within the period for which the samples are stable at –70° C. The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Thirty-six subjects (26 males and 10 females) were enrolled in the study and received investigation product. The mean age of the subjects was 31.4 years of age, and the range was 21 to 46 years old. Thirty-two subjects completed the study and were eligible for pharmacokinetic analysis. Two subjects withdrew due to adverse events during Period 1, 1 subject withdrew due to difficult blood draws, and 1 subject withdrew for personal reasons. An additional subject was not included in the pharmacokinetic analysis population due to vomiting. The demographics of the thirty-one subjects included in the pharmacokinetic analysis population are shown below.

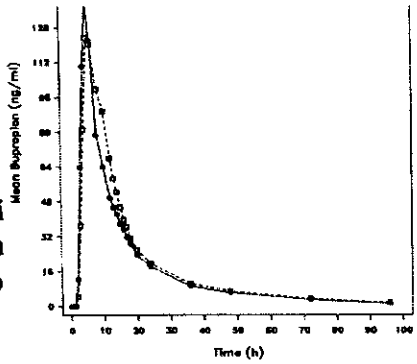
Table 4. Demographics of Subjects Included in the Pharmacokinetic Analysis Population

Mean Age (Range)	Gender	Weight (mean ± SD)	Race
31.8 (21-46)	23 males 8 females	75.1 ± 9.4 kg (n=31) 78.8 ± 6.9 kg (male) 64.4 ± 7.1 kg (female)	Asian 2 Black 6 Caucasian 23

Pharmacokinetics

In addition to evaluation of the pharmacokinetics of the parent compound and its active metabolites, the pharmacological activity-weighted composite (PAWC) was also evaluated. The PAWC was calculated by dividing the measured concentrations by the respective molecular weight of each moiety followed by multiplication by the previously determined relative potency in an animal model of antidepressant activity. The sum of the resultant values represents the PAWC.

Pharmacokinetic parameters were determined using noncompartmental analysis. The plasma concentration time course and the pertinent pharmacokinetic parameters for bupropion, its metabolites, and the PAWC are shown in Figure 1 and Tables 5 and 6, below.

Fi 

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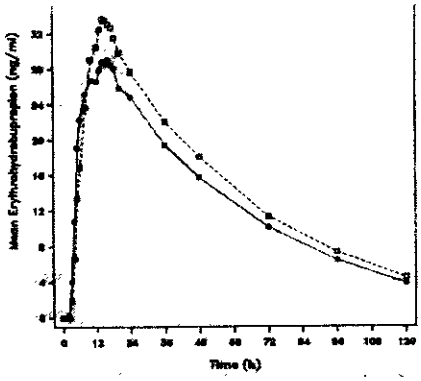

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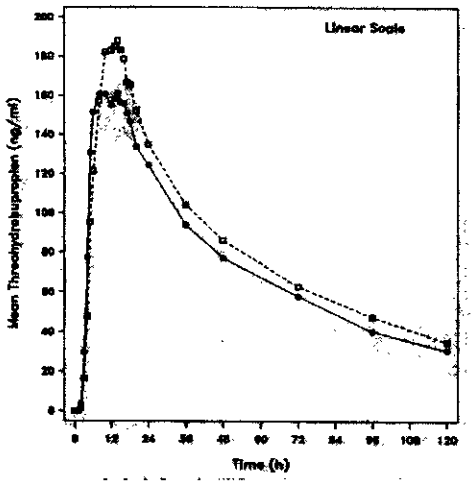

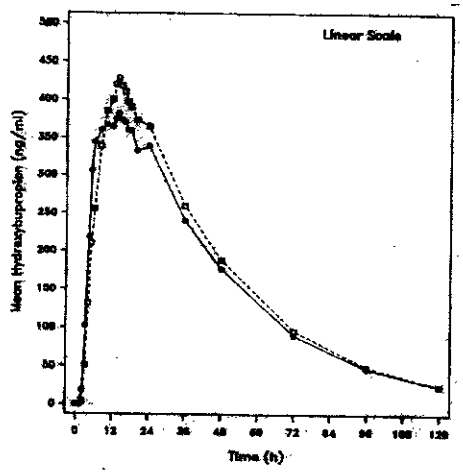

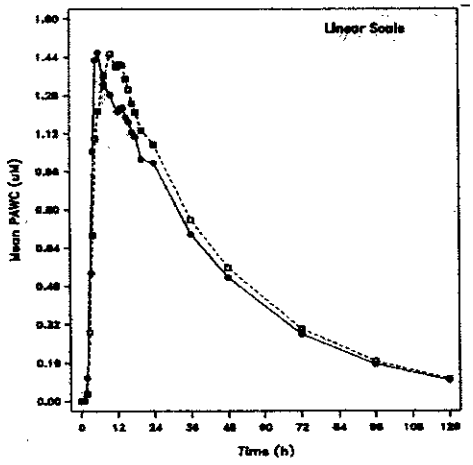

Table 5. Pharmacokinetic parameters (arithmetic mean) for bupropion and metabolites (Study 2548)

	Test (Fed) (% CV) n=31	Reference (Fasting) (% CV) n=31
Bupropion		
t_{max} (h)[a]	5.07 (4.00-12.00)	5.00 (4.00 – 8.00)
C_{max} (ng/mL)	[redacted] (31)	[redacted] (32)
AUC $_{0-t}$ (ng*h/mL)	1775.4 (30)	1628.4 (31)
AUC $_{0-\infty}$ (ng*h/mL)	1832.5 (30)	1678.4 (31)
$t_{1/2}$ (hr)	21.8 (27)	21.2 (29)
λ_z (hr^{-1})	0.0347 (32)	0.0359 (34)
Bupropion Erythroamino Alcohol		
t_{max} (h)[a]	14.00 (8.00 – 24.02)	15.00 (5.00 – 24.00)
C_{max} (ng/mL)	[redacted] (26)	[redacted] (32)
AUC $_{0-t}$ (ng*h/mL)	1803 (38)	1634.6 (45)
AUC $_{0-\infty}$ (ng*h/mL)	2116.0 (48)	1867.7 (52)
$t_{1/2}$ (hr)	35.2 (34)	33.9 (33)
λ_z (hr^{-1})	0.0215 (27)	0.0223 (28)
Bupropion Threoamino Alcohol		
t_{max} (h)[a]	8.00 (4.00 – 24.00)	13.00 (6.00 – 18.00)
C_{max} (ng/mL)	[redacted] (47)	[redacted] (55)
AUC $_{0-t}$ (ng*h/mL)	9769.7 (63)	9032.2 (73)
AUC $_{0-\infty}$ (ng*h/mL)	13280.6 (71)	11696.3 (77)
$t_{1/2}$ (hr)	55.2 (32)	55.2 (38)
λ_z (hr^{-1})	0.0139 (30)	0.0139 (32)
Hydroxybupropion		
t_{max} (h)[a]	14.00 (8.00 – 24.02)	14.00 (5.00 - 24.00)
C_{max} (ng/mL)	[redacted] (40)	[redacted] (38)
AUC $_{0-t}$ (ng*h/mL)	19733.5 (48)	18939.8 (44)
AUC $_{0-\infty}$ (ng*h/mL)	20886.1 (49)	19852.7 (46)
$t_{1/2}$ (hr)	24.1 (22)	24.0 (20)
λ_z (hr^{-1})	0.0301 (22)	0.0302 (23)
PAWC		
t_{max} (h)[a]	10.00 (5.00 – 17.00)	6.00 (4.00 – 14.00)
C_{max} (µM)	[redacted] (33)	[redacted] (27)
AUC $_{0-t}$ (µM*h)	63.3 (42)	60.1 (40)
AUC $_{0-\infty}$ (µM*h)	68.0 (43)	63.8 (41)
$t_{1/2}$ (hr)	27.6 (22)	27.2 (26)
λ_z (hr^{-1})	0.0263 (22)	0.0271 (24)

[a] median (range)

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Table 6. Bioequivalence Assessment for AK1BIOVAIL2548

	Geometric Mean		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	Reference	Test		
Bupropion				
C_{max} (ng/ml)	143.2	132.2	0.92	(0.84, 1.01)
AUC $_{0-t}$ (ng*h/ml)	1540.5	1696.2	1.10	(1.04, 1.17)
AUC $_{0-\infty}$ (ng*h/ml)	1589.8	1751.4	1.10	(1.04, 1.16)
Bupropion Erythroamino Alcohol				
C_{max} (ng/ml)	29.3	34.6	1.18	(1.10, 1.26)
AUC $_{0-t}$ (ng*h/ml)	1476.7	1674.5	1.13	(1.04, 1.24)
AUC $_{0-\infty}$ (ng*h/ml)	1648.1	1902.6	1.15	(1.05, 1.27)
Bupropion Threoamino Alcohol				
C_{max} (ng/ml)	159.0	186.9	1.18	(1.11, 1.25)
AUC $_{0-t}$ (ng*h/ml)	7511.6	8444.8	1.15	(1.04, 1.26)
AUC $_{0-\infty}$ (ng*h/ml)	9568.3	10969.0	1.12	(1.04, 1.21)
Hydroxybupropion				
C_{max} (ng/ml)	378.5	416.3	1.10	(1.03, 1.17)
AUC $_{0-t}$ (ng*h/ml)	17054.3	17695.7	1.05	(0.96, 1.12)
AUC $_{0-\infty}$ (ng*h/ml)	17786.1	18601.3	1.04	(0.97, 1.13)
PAWC				
C_{max} (µM)	1.49	1.5	1.02	(0.97, 1.08)
AUC $_{0-t}$ (µM*h)	55.3	58.2	1.06	(0.98, 1.13)
AUC $_{0-\infty}$ (µM*h)	58.3	61.9	1.05	(0.99, 1.14)

Reanalysis of the data by the reviewer was in agreement with that provided by the sponsor regarding the bioequivalence during the test and reference periods.

No evidence of dose dumping after administration with food was observed, with C_{max} for bupropion in both periods occurring at approximately 5 hours, in agreement with t_{max} observed in the previous single dose and multiple dose studies of WELLBUTRIN XL (AK1BIOVAIL2751 and AK1BIOVAIL2543).

The 90% confidence intervals on the geometric means of the C_{max} and AUC ratios are within the bioequivalence interval of 0.8 to 1.25 for bupropion and for the predominant metabolite hydroxybupropion. They are outside of the bioequivalence interval for the Cmax and AUC $_{0-\infty}$ for bupropion erythroamino [redacted] and (1.05, 1.27), respectively, and the AUC $_{0-t}$ for bupropion threoamino alcohol (1.04, 1.26). This was due to an approximate [redacted] and 13% increase in bupropion erythroamino Cmax and $AUC_{0-\infty}$, respectively and an approximate 8% increase in bupropion threoamino AUC $_{0-t}$.

The Sponsor has noted a significant sequence effect for Cmax for bupropion. The source of this effect is unknown. The sequences were balanced with respect to age, race, weight and body mass index. There were fewer women in Sequence AB than in Sequence BA. All concentrations of bupropion at the beginning of the second period were BQL. Thus the sequence effect is not due to carryover of bupropion.

Safety

The adverse effect profiles during the test and reference periods were similar. Approximately 12 % of subjects in either the test or reference periods experienced a drug-related adverse event. Adverse events included headache, hand numbness, tremor, pruritis, and nausea and vomiting. Two subjects withdrew from the study due to adverse events. In one case the subject had swelling, pain, stiffness, and numbness in the right hand, and in the other case the subject had contusion at the venipuncture site and upper limb that were considered to be unrelated to the study drug or unlikely related to the study drug.

CONCLUSIONS:

Although the 90% Confidence interval is not contained in the equivalence limits of 80%-125% for 2 of the metabolites of bupropion, the differences between the fed and fasting states are very small (≤ 15%). Therefore, this study demonstrates that there is no appreciable effect of food on exposure to bupropion or its metabolites when bupropion extended release tablets (300 mg) are given with a high fat meal.

6.2.3 DOSAGE STRENGTH EQUIVALENCE

A TWO-WAY, CROSSOVER, OPEN-LABEL, SINGLE DOSE, FASTING, DOSAGE STRENGTH EQUIVALENCY STUDY OF TWO STRENGTHS (150 MG AND 300 MG) OF BUPROPION HCL EXTENDED RELEASE TABLETS GIVEN ONCE DAILY IN NORMAL HEALTHY NON-SMOKING MALE AND FEMALE SUBJECTS

Study Investigators and Site:
Paul Y. Tam, MD, FRCP, FACP
Biovail Contract Research
Toronto, Ontario, Canada

Protocol Number: AK1BIOVAIL2571

OBJECTIVES:

To investigate the dosage strength equivalency of the 150 mg and 300 mg product strengths of bupropion hydrochloride extended release tablets under fasting conditions.

FORMULATIONS:

Table 1. Product used in AK1BIOVAIL2571

	Package Lot Number	Dose Form Lot Number	Date of Manufacture (Dates of Study)
Bupropion HCl 150 mg extended release tablets (Biovail Corporation, Canada)	02A063	01M174	November 2001 January 24, 2002 – March 19, 2002
Bupropion HCl 300 mg extended release tablets (Biovail Corporation, Canada)	01L238	01L088	October 2001 January 24, 2002 – March 19, 2002

Long-term stability studies were ongoing at the time of this review. The product appeared to be stable for 6-9 months.

STUDY DESIGN:

This study was a single dose, open-label, randomized, 2-period, 2-treatment, 2-sequence crossover study, as shown in Table 1, below. For Treatment A, subjects received a single dose of (2) bupropion HCl extended release 150 mg tablets (test). For Treatment B, subjects received a single dose of bupropion HCl extended release 300 mg tablet (reference). Study drug was given with 240 ml of room temperature water following an overnight fast of at least 10 hours. Additional water was not allowed from 1 hour pre-dose until 1 hour after dose. Standardized meals were provided with beverages at 4.5 and 9.5 hours after the dose, and an additional standardized snack was provided at 13.5 hours after the dose. Meals and beverages were to be free of grapefruit products, xanthine, and caffeine and were to be identical in each study period. There was to be at least a 3-week washout period between study periods.

Table 2. Treatment Sequence in AK1BIOVAIL2571

Sequence Number	Treatment Period 1	Treatment Period 2
1	A (T)	B (R)
2	B (R)	A (T)

Inclusion criteria included healthy nonsmoking males or females, 18 to 55 years of age. Exclusion criteria included use of prescription medication (including monoamine oxidase inhibitors) within 14 days and over-the-counter medication within 7 days prior to the study. Oral contraceptives or contraceptive implants were not allowed within 30 days and depot injection of a progestogen drug was not allowed within 1 year prior to investigational product administration.

Subjects were asked to abstain from alcohol, grapefruit juice, caffeine, and xanthine-containing foods and fluids from 48 hours prior to the start of the study period until the final blood draw.

Blood samples were collected at fixed times and plasma stored at –70° C until analyzed. Samples were collected at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0, and 120 hours post-drug administration.

ASSAY:

Table 3. Performance of Analytical Method for AK1BIOVAIL2571

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-day CV (%)	Inter-day Accuracy (%)
Bupropion	LC/MS/MS					7.1	
						5.0	
						4.0	
						3.3	
Bupropion Erythroamino alcohol	LC/MS/MS					6.4	
						5.0	
						3.2	
						2.8	
Bupropion Threoamino Alcohol	LC/MS/MS					7.0	
						4.8	
						3.0	
						3.0	
Hydroxybupropion	LC/MS/MS					5.3	
						4.2	
						3.4	
						3.8	

Two calibration curves and duplicate QC samples (at 4 concentration levels) were analyzed with each batch of study samples. At least 6 out of 8 QC samples were within [redacted] of their respective nominal value, except for 1 run for bupropion in which 5 out of 8 samples were within [redacted] of the nominal value. Study samples were stored at –70° C. Samples were analyzed within the period for which the samples are stable at –70° C. The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Thirty-six subjects (19 males and 17 females) were enrolled in the study and received investigation product. The mean age of the subjects was 34.2 years of age, and the range was 19 to 55 years old. One subject withdrew for personal reasons. Thirty-five subjects completed the study and were eligible for pharmacokinetic analysis. The demographics of the thirty-five subjects included in the pharmacokinetic analysis population are shown below.

Table 4. Demographics of Subjects Included in the Pharmacokinetic Analysis Population

Mean Age (Range)	Gender	Weight (mean ± SD)	Race
34.3 (19-55)	19 males 16 females	72.9 ± 11.2 kg (n=35) 79.3 ± 10.4 kg (male) 65.4 ± 6.5 kg (female)	Asian 4 Black 4 Caucasian 27

Pharmacokinetics

In addition to evaluation of the pharmacokinetics of the parent compound and its active metabolites, the pharmacological activity-weighted composite (PAWC) was also evaluated. The PAWC was calculated by dividing the measured concentrations by the respective molecular weight of each moiety followed by multiplication by the previously determined relative potency in an animal model of antidepressant activity. The sum of the resultant values represents the PAWC.

Pharmacokinetic parameters were determined using noncompartmental analysis. The plasma concentration time course and the pertinent pharmacokinetic parameters (provided by Sponsor) for bupropion, its metabolites, and the PAWC are shown in Figure 1 and Tables 5 and 6, below.

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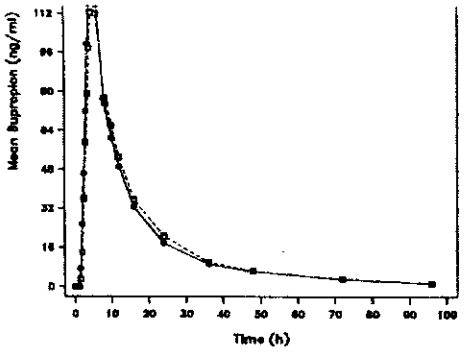
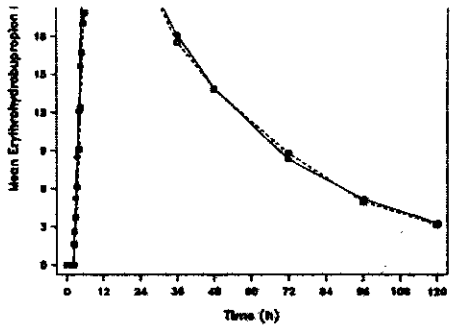
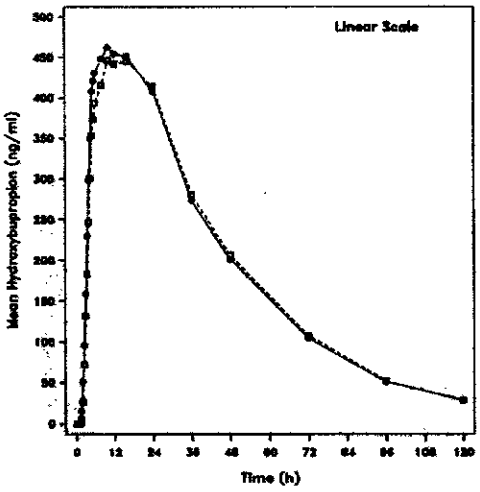
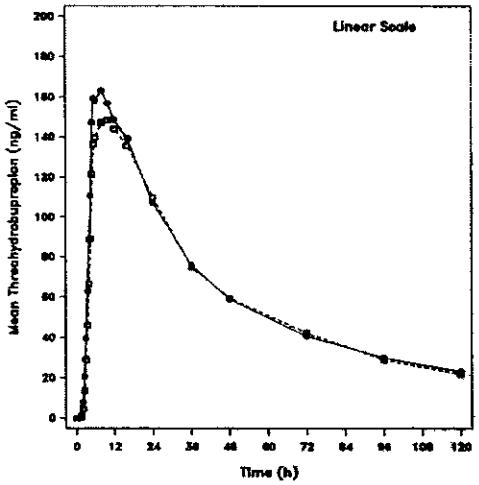








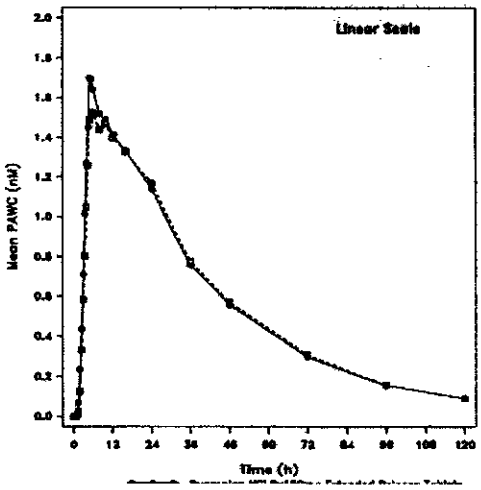


Table 5. Pharmacokinetic parameters (arithmetic mean) for bupropion and metabolites (Study 2571)

	Test (2x 150 mg tablets) (% CV) n=35	Reference (300 mg tablet) (% CV) n=35
Bupropion		
t_{max} (h)[a]	5.00 (3.5 - 8.00)	5.00 (4.00 - 8.00)
C_{max} (ng/mL)	[redacted] (25)	[redacted] (32)
AUC $_{0-t}$ (ng*h/mL)	1648.9 (29)	1676.6 (28)
AUC $_{0-\infty}$ (ng*h/mL)	1702.7 (29)	1728.3 (28)
$t_{1/2}$ (hr)	22.7 (33)	21.8 (34)
λ_z (hr^{-1})	0.0355 (49)	0.0373 (49)
Bupropion Erythroamino Alcohol		
t_{max} (h)[a]	16.00 (6.00 - 16.15)	16.00 (5.50 - 24.00)
C_{max} (ng/mL)	[redacted] (23)	[redacted] (24)
AUC $_{0-t}$ (ng*h/mL)	1508.8 (40)	1441.8 (34)
AUC $_{0-\infty}$ (ng*h/mL)	1702.7 (46)	1613.6 (39)
$t_{1/2}$ (hr)	32.2 (27)	32.1 (29)
λ_z (hr^{-1})	0.0232 (29)	0.0232 (26)
Bupropion Threoamino Alcohol		
t_{max} (h)[a]	8.00 (5.00 - 16.00)	8.00 (5.00 - 16.00)
C_{max} (ng/mL)	[redacted] (35)	[redacted] (36)
AUC $_{0-t}$ (ng*h/mL)	7548.1 (48)	7262.9 (42)
AUC $_{0-\infty}$ (ng*h/mL)	9428.7 (53)	9091.3 (43)
$t_{1/2}$ (hr)	50.5 (33)	51.5 (33)
λ_z (hr^{-1})	0.0150 (31)	0.0149 (33)
Hydroxybupropion		
t_{max} (h)[a]	10.00 (5.00 - 24.17)	12.00 (6.00 - 24.00)
C_{max} (ng/mL)	[redacted] (37)	[redacted] (36)
AUC $_{0-t}$ (ng*h/mL)	22506.3 (42)	22380.3 (39)
AUC $_{0-\infty}$ (ng*h/mL)	23634.2 (44)	23498.8 (41)
$t_{1/2}$ (hr)	24.0 (20)	24.1 (19)
λ_z (hr^{-1})	0.0301 (23)	0.0298 (19)
PAWC		
t_{max} (h)[a]	5.50 (4.00 - 12.00)	5.50 (4.50 - 24.00)
C_{max} (µM)	[redacted] (24)	[redacted] (27)
AUC $_{0-t}$ (µM*h)	67.3 (35)	66.8 (33)
AUC $_{0-\infty}$ (µM*h)	71.0 (37)	70.4 (34)
$t_{1/2}$ (hr)	25.9 (20)	25.9 (19)
λ_z (hr^{-1})	0.0281 (24)	0.0278 (21)

[a] median (range)

Reanalysis of this data by the reviewer was in agreement with the results presented by the Sponsor, differing in only AUC $_{0-\infty}$, $t_{1/2}$, and λ_z by less than 5%.

Table 6. Bioequivalence Assessment for AK1BIOVAIL2571

	Geometric Mean		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	Reference	Test		
Bupropion				
C_{max} (ng/ml)	139.5	145.1	1.04	(0.98, 1.10)
AUC $_{0-t}$ (ng*h/ml)	1610.9	1583.4	0.98	(0.94, 1.03)
AUC $_{0-\infty}$ (ng*h/ml)	1663.6	1636.1	0.98	(0.94, 1.03)
Bupropion Erythroamino Alcohol				
C_{max} (ng/ml)	26.77	28.2	1.05	(0.99, 1.11)
AUC $_{0-t}$ (ng*h/ml)	1360.3	1405.1	1.03	(0.97, 1.10)
AUC $_{0-\infty}$ (ng*h/ml)	1499.9	1555.1	1.04	(0.97, 1.11)
Bupropion Threoamino Alcohol				
C_{max} (ng/ml)	152.9	163.6	1.07	(1.00, 1.14)
AUC $_{0-t}$ (ng*h/ml)	6724.6	6905.2	1.03	(0.97, 1.09)
AUC $_{0-\infty}$ (ng*h/ml)	8325.6	8427.7	1.04	(0.95, 1.09)
Hydroxybupropion				
C_{max} (ng/ml)	446.7	459.5	1.03	((0.98, 1.08)
AUC $_{0-t}$ (ng*h/ml)	20679.9	20674.3	1.00	(0.94, 1.06)
AUC $_{0-\infty}$ (ng*h/ml)	21631.2	21573.2	1.00	(0.94, 1.06)
PAWC				
C_{max} (μM)	152.9	163.6	1.06	(1.00, 1.12)
AUC $_{0-t}$ (μM*h)	6724.6	6905.2	1.00	(0.95, 1.06)
AUC $_{0-\infty}$ (μM*h)	8325.6	8437.8	1.00	(0.95, 1.06)

Reanalysis of the data by the reviewer was in agreement with that provided by the sponsor regarding the bioequivalence between the test and reference treatments.

The 90% confidence intervals on the geometric means of the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ ratios are within the bioequivalence interval of 0.80 to 1.25.

Safety

Approximately 17 % of subjects in either the test or reference periods experienced a drug-related adverse event. Headache was the most common drug-related adverse event and occurred to a similar extent in both treatments.

CONCLUSIONS:

This study has demonstrated equivalence between bupropion extended release given as a single 300 mg tablet and a single dose of bupropion extended release given as 2x150 mg tablets. Thus, dosage strength equivalence has been demonstrated.

6.2.4 BIOEQUIVALENCE STUDY

A TWO-WAY, CROSSOVER, STEADY STATE, MULTIPLE-DOSE OPEN-LABEL FASTING COMPARATIVE BIOAVAILABILITY STUDY OF BUPROPION HCL 300 MG EXTENDED-RELEASE TABLETS (1X300 MG Q.D.) VERSUS WELLBUTRIN 100 MG TABLETS (TID) IN NORMAL HEALTHY NON-SMOKING MALE AND FEMALE SUBJECTS

Study Investigators and Site:

Paul Y. Tam, MD, FRCP, FACP
Biovail Contract Research
Toronto, Ontario, Canada

Protocol Number: AK1BIOVAIL2543

OBJECTIVES:

To evaluate the bioavailability of a once-daily bupropion hydrochloride (HCl) extended release tablet test formulation (1x300 mg q.d., Lot Number 01K211) relative to reference WELLBUTRIN tablets (1x 100 mg tid) under steady-state, fasting conditions.

FORMULATIONS:

Table 1. Products used in AK1BIOVAIL2543

	Package Lot Number	Dose Form Lot Number	Date of Manufacture (Dates of Study)
Test Product (T) Bupropion HCl 300 mg extended release tablets(Biovail Corporation, USA)	01K211	01L088	October 2001 (October 29, 2001 – December 10, 2001)
Reference Product (R) WELLBUTRIN 100 mg tablets ([redacted] GlaxoSmithKline)	1A2494	_	Exp Date 3/2003

The batch size for the test product was [redacted] tablets. This represents approximately [redacted] of the proposed commercial batch size of [redacted]. Stability studies were ongoing at the time of the review. According to the Sponsor, the test product was stable for at least 9 months.

STUDY DESIGN:

This study was an open-label, randomized, 2-period, 2-treatment, 2-sequence crossover multiple dose, steady-state study, as shown in Table 1, below. For Treatment A, subjects received WELLBUTRIN 100 mg bid on day 1, 2, and 3 (beginning at 7AM), and received bupropion 300 mg (extended release tablet) daily on the mornings of Days 4 to 13 (treatment period T). For Treatment B, subjects received WELLBUTRIN 100 mg bid (beginning at 7AM) on days 1, 2, and 3 and WELLBUTRIN 100 mg tid (at 0, 6, and 12 hours beginning at 7AM) on Days 4 to 13 (treatment period R). There was a minimum interval of 2 weeks between the last dose of Day 13

in the first treatment period and the first dose of the second period. The 300 mg dose of the extended release product is the highest proposed dosage strength of this product.

Table 2. Treatment Sequence in AK1BIOVAIL2543

Sequence Number	Treatment Period 1	Treatment Period 2
1	A (T)	B (R)
2	B (R)	A (T)

Inclusion criteria included healthy nonsmoking males or females, 18 years of age and older. Exclusion criteria included use of prescription medication (including monoamine oxidase inhibitors) within 14 days and over-the-counter medication within 7 days prior to the study. Oral contraceptives or contraceptive implants were not allowed within 30 days and depot injection of progestogen drug was not allowed within 1 year prior to investigational product administration.

The morning doses of study drugs were administered with 240 ml of room temperature water after an overnight fast of at least 10 hours. The other doses during the day were given with 240 ml of room temperature water after a fast of at least 1 hour. Subjects were asked to abstain from alcohol, grapefruit juice, caffeine, and xanthine-containing foods and fluids from 48 hours prior to the start of the study period until the final blood draw. Blood samples were collected at fixed times and plasma stored at –70° C until analyzed. On days 1, 10, 11, and 12 of both treatment periods, samples were collected at 0.0 hr (pre-dose). For Treatment A, blood samples were collected on Day 13 at 0 hours (pre-dose) and 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, and 24 hours after administration of study drug. For Treatment B, blood samples were collected on Day 13 at 0 hr (Pre-dose), 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0 (before study drug administration), 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, 12.0 (before study drug administration), 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, 16.0, 17.0, 18.0, 20.0, 22.0, and 24.0 hours after the 0.0 hour study drug administration.

ASSAY:

Table 3. Performance of Analytical Method for AK1BIOVAIL2543

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-day CV (%)	Inter-day Accuracy (%)
Bupropion	LC/MS/MS					6.0 3.8 3.4 3.5	
Bupropion Erythroamino alcohol	LC/MS/MS					8.2 4.7 3.9 3.5	
Bupropion Threoamino Alcohol	LC/MS/MS					10.2 5.3 4.1 3.7	
Hydroxybupropion	LC/MS/MS					6.9 3.7 3.3 3.6	

Two calibration curves and duplicate QC samples were analyzed with each batch of study samples. Study samples were stored at –70° C. Samples were analyzed within the period for which the samples are stable at –70° C. Methanolic solutions of bupropion and metabolites were used within the period for which they were stable. The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Forty subjects (27 males and 13 females) were enrolled in the study. The mean age of the subjects was 32.9 years of age, and the range was 20 to 50 years old. Thirty subjects completed the entire study and were eligible for pharmacokinetic analysis. Nine subjects discontinued from the study due to adverse events and a 10th subject declined to participate further after Day 6 of Period 1.

Table 4. Demographics of Subjects Completing the Study

Mean Age (Range)	Gender	Weight (mean ± SD)	Race
34 (20-50)	22 males 8 females	72.10 ± 10.0 kg (n=30) 74.7 ± 8.8 kg (male) 64.9 ± 10.1 kg (female)	Asian 2 Black 10 Caucasian 18

Pharmacokinetics

In addition to evaluation of the pharmacokinetics of the parent compound and its active metabolites, the pharmacological activity-weighted composite (PAWC) was also evaluated. The

PAWC was calculated by dividing the measured concentrations by the respective molecular weight of each moiety followed by multiplication by the previously determined relative potency in an animal model of antidepressant activity. The sum of the resultant values represents the PAWC.

Evaluation of trough concentration values for the last 3 days of dosing (Days 11, 12, and 13) determined that steady state was achieved.

Pharmacokinetic parameters were determined using noncompartmental analysis. The plasma concentration time course and the pertinent pharmacokinetic parameters for bupropion, its metabolites, and the PAWC are shown in Figure 1 and Tables 5 and 6, below.

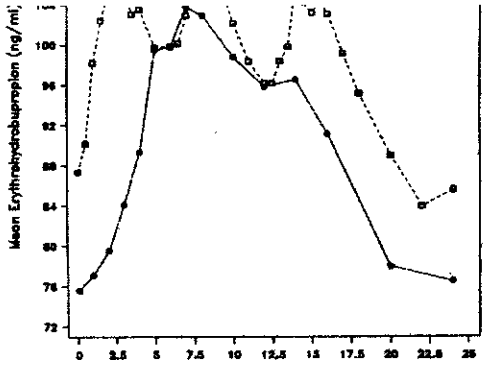
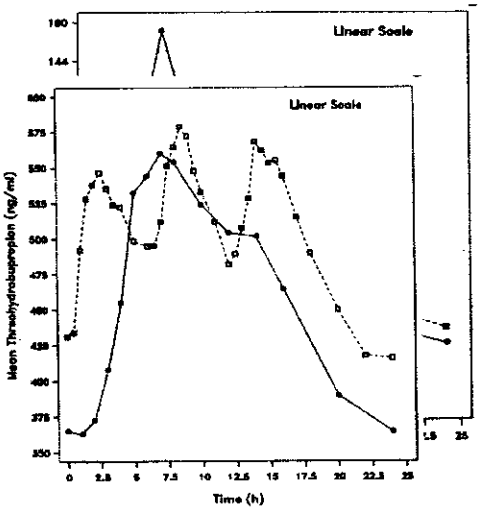
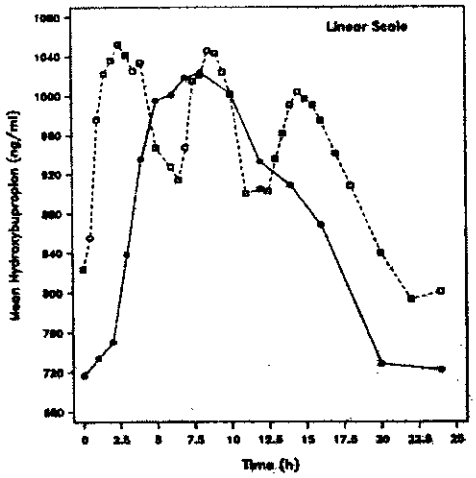


Figure 1. Mean Plasma Concentration Time Course for Buprop
Administration of Test (solid circles) or Reference (open squares)





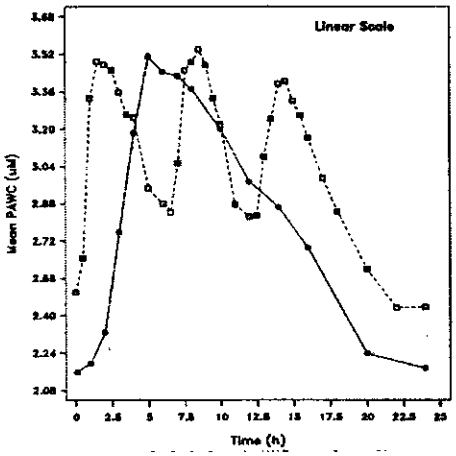


Table 5. Pharmacokinetic parameters (arithmetic mean) for bupropion and metabolites (Study 2543)

	Test (Bupropion XL) (% CV) n=30	**Reference (Wellbutrin)** (% CV) n=30
Bupropion		
t_{max} (h)[a]	5.00 (3.00-7.00)	1.50 (1.00-3.00)
C_{max} (ng/mL)	[redacted] (28)	[redacted] (32)
AUC $_{0-24}$ (ng*h/mL)	1612.0 (30)	1792.0 (27)
C_{min} (ng/ml)	27.6 (39)	34.1 (37)
Cav (ng/ml)	67.2 (30)	74.7 (27)
Degree of Fluctuation (%)	212.6 (19)	190.0 (21)
Swing (%)	554.6 (35)	439.6 (32)
Bupropion Erythroamino Alcohol		
t_{max} (h)[a]	8.00 (5.00-14.00)	2.50 (1.07-3.50)
C_{max} (ng/mL)	[redacted] (27)	[redacted] (22)
AUC $_{0-24}$ (ng*h/mL)	2145.7 (29)	2353.7 (27)
C_{min} (ng/ml)	76.5 (34)	85.6 (31)
Cav (ng/ml)	89.4 (29)	98.1 (27)
Degree of Fluctuation (%)	38.1 (40)	38.9 (87)
Swing (%)[b]	46.0 (35)	46.2 (94.7)
Bupropion Threoamino Alcohol		
t_{max} (h)[a]	8.00 (5.00-14.00)	2.50 (1.07-5.00)
C_{max} (ng/mL)	[redacted] (27)	[redacted] (22)
AUC $_{0-24}$ (ng*h/mL)	10987.9 (29)	12051.4 (26)
C_{min} (ng/ml)	364.4 (34)	415.7 (29)
Cav (ng/ml)	457.8 (29)	502.1 (26)
Degree of Fluctuation (%)	50.5 (34)	45.2 (48)
Swing (%)[b]	65.7 (40)	56.3 (52)
Hydroxybupropion		
t_{max} (h)[a]	7.00 (4.00-14.00)	2.50 (1.00-4.00)
C_{max} (ng/mL)	[redacted] (35)	[redacted] (29)
AUC $_{0-24}$ (ng*h/mL)	20824.8 (36)	22456.1 (31)
C_{min} (ng/ml)	722.2 (39)	800.9 (33)
Cav (ng/ml)	867.7 (36)	935.7 (31)
Degree of Fluctuation (%)	44.3 (37)	40.8 (77)
Swing (%)[b]	54.6 (41)	49.2 (83)
PAWC		
t_{max} (h)[a]	6.00 (4.00-14.00)	2.00 (1.00-3.00)
C_{max} (µM)	[redacted] (25)	[redacted] (22)
AUC $_{0-24}$ (µM*h)	66.5 (27)	72.1 (23)
C_{min} (µM)	2.2 (32)	2.4 (26)
Cav (µM)	2.8 (27)	3.0 (23)
Degree of Fluctuation (%)	57.7 (21)	50.1 (36)
Swing (%)[b]	75.2 (35)	62.9 (39)

[a] median (range)
[b] calculated by reviewer

Table 6. Bioequivalence Assessment for Study 2543

	Geometric Mean		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	Reference	Test		
Bupropion				
C_{max} (ng/ml)	165.2	160.1	0.97	(0.91, 1.03)
C_{min} (ng/ml)	31.6	25.4	0.80	(0.76, 0.85)
AUC_{0-24} (ng*h/ml)	1714.3	1531.4	0.89	(0.86, 0.93)
Bupropion Erythroamino Alcohol				
C_{max} (ng/ml)	116.5	105.0	0.90	(0.85, 0.96)
C_{min} (ng/ml)	81.6	72.4	0.89	(0.84, 0.94)
AUC_{0-24} (ng*h/ml)	2263.5	2057.9	0.91	(0.87, 0.95)
Bupropion Threoamino Alcohol				
C_{max} (ng/ml)	612.5	564.8	0.92	(0.87, 0.97)
C_{min} (ng/ml)	397.3	344.3	0.87	(0.82, 0.92)
AUC_{0-24} (ng*h/ml)	11609.0	10520.7	0.91	(0.87, 0.94)
Hydroxybupropion				
C_{max} (ng/ml)	1111.4	1030.0	0.93	(0.86, 1.00)
C_{min} (ng/ml)	758.8	669.0	0.88	(0.84, 0.93)
AUC_{0-24} (ng*h/ml)	21432.6	19528.1	0.91	(0.87, 0.95)
PAWC				
C_{max} (µM)	3.8	3.6	0.95	(0.90, 0.99)
C_{min} (µM)	2.4	2.1	0.88	(0.83, 0.92)
AUC_{0-24} (µM*h)	70.1	63.8	0.91	(0.88, 0.95)

No evidence of dose dumping was observed after administration of WELLBUTRIN XL.

Reanalysis of the data by the reviewer was in agreement with that provided by the sponsor regarding the pharmacokinetic parameters as well as the bioequivalence of the test and reference compounds.

The 90% confidence intervals on the geometric means of the C_{max}, C_{min}, and AUC_{0-24} ratios are within the bioequivalence interval of 0.8 to 1.25 for bupropion and its metabolites as well as the PAWC, with the exception of bupropion C_{min} that was approximately 19% lower than that of the Reference formulation.

Safety

The adverse effect profiles for the test and reference products were similar. Adverse events in the run-in period included headache, constipation, nausea, dizziness, tremor, lightheadedness, gastric upset, chest pain, epistaxis, back pain, rash on chest, palpitations, increased creatinine levels, and increased alanine aminotransferase levels. After the run-in period, the most common drug-related adverse events were headache, constipation, nausea, and dizziness. More than half

of the subjects experienced a drug-related adverse event (57% while receiving the test product and 63% while receiving the reference product). The most common adverse events that led to premature discontinuation of the investigation product or the study were skin events including rash and pruritis that were considered to be mild to moderate in severity. Other adverse events in the subjects who discontinued the study included dysuria or urinary urgency, dizziness, and nausea. One subject had chest pain and an abnormal ECG that were considered to be unlikely related to study medication.

CONCLUSIONS:

This study demonstrated equivalence between bupropion extended release (Test) 300 mg tablets and WELLBUTRIN immediate release (Reference) tablets (100 mg tid) after multiple dosing at steady state under fasting conditions for all comparisons except for C_{min} for the parent compound. Consideration should be given to the active metabolites, since they account for approximately 90% of the systemic exposure. Since the two products are bioequivalent in terms of the metabolites and for C_{max} and AUC of the parent bupropion, it is reasonable to suggest that the two products are comparable in exposure.

6.2.5 BIOANALYTICAL METHOD

Bioanalytical Method for Bupropion and Its Metabolites in NDA 21-515

A liquid chromatography [redacted] mass spectrometry (LC-MS/MS) assay was used for analysis of bupropion and its metabolites, bupropion erythroamino alcohol, bupropion threoamino alcohol, and hydroxybupropion in human plasma.

[redacted]

Standard operating procedures (SOPs) were in place for sample preparation, the analytical procedure, for acceptance of the bioanalytical run (system suitability and acceptance of calibration standards and quality control (QC) samples), and acceptance criteria for subject samples, including sample dilution.

Selectivity, Accuracy, Precision, and Recovery

[redacted]

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

In conclusion, the bioanalytical method used for analysis of plasma samples in the clinical studies in NDA 21-515 is considered adequately documented and validated.

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/s/

Sally Yasuda
5/12/03 01:38:36 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
5/12/03 01:47:42 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW
AMENDMENT

NDA:	21-515
Sponsor:	GlaxoSmithKline
Drug:	Extended Release Tablets
Proposed Indication:	Major Depressive Disorder
Material Submitted:	DSI Inspection of Study AK1BIOVAIL2543
Correspondence Date:	August 26, 2002
Reviewer:	Sally Usdin Yasuda, MS, PharmD

Background:

The Office of Clinical Pharmacology and Biopharmaceutics requested a Division of Scientific Investigations (DSI) inspection of the pivotal bioequivalence study in this NDA submission. The clinical and analytical portions of this study were conducted at Biovail Contract Research in Toronto, Ontario, Canada. Due to the SARs outbreak in Canada, the study documents were transported to Biovail Technologies Ltd. in Chantilly, VA for regulatory review.

The DSI found that the analytical report did not accurately reflect the source data for subject 26, in which the erythrohydrobupropion (also referred to as bupropion erythroamino alcohol) results were shifted by several time points beginning at the 7.5 hour time point on Day 13 of period 2 (Wellbutrin 100 mg tid) and incorrectly transcribed to the analytical report. The DSI provided the actual concentrations.

Current Review:

These correct data for period 2 for subject 26 were used by the Office of Clinical Pharmacology and Biopharmaceutics to re-evaluate the bioequivalence comparison for this metabolite. The C_{min} (corrected) is 80.9 (33) ng/ml and was previously calculated as 85.6 (31) ng/ml, (mean, CV). The AUC_{0-t} (corrected) is 2350.5 (28) ng*hr/ml and was previously calculated as 2353.7 (27) ng*hr/ml, (mean, CV). There was no change in the C_{max}. These changes did not result in any changes in the ratio of geometric means or the 90% confidence interval for the ratio of geometric means, and therefore remain within the bioequivalence interval of 0.8 to 1.25.

Note: the reviewer made a typographical error in the original review in reporting the C_{max} for bupropion erythroamino alcohol (reference) as [redacted] and it should have been [redacted] This was a typographical error in the report and did not affect the BE calculations.

Conclusions and Recommendations:

From the perspective of Clinical Pharmacology and Biopharmaceutics, data as provided by the DSI have been used to re-evaluate bioequivalence for bupropion XL and Wellbutrin (IR) for the erythrohydrobupropion metabolite. The results still demonstrate bioequivalence on the 90% confidence intervals of the ratio of the geometric means of the pertinent PK parameters for Wellbutrin XL compared to Wellbutrin (IR) at steady state.

Sally Usdin Yasuda, MS, PharmD
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana Uppoor, PhD
Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-120 NDA 21515
CSO/D. Bates
/Biopharm/S. Yasuda
/TL Biopharm/R. Uppoor
HFD-860 /DD DPE1/M. Mehta/C. Sahajwalla

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/s/

Sally Yasuda
6/20/03 07:41:04 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
6/20/03 05:23:20 PM
BIOPHARMACEUTICS