CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-711

MEDICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 **Tel:(301)443-3741**

NDA 20-711
SPONSOR: Glaxo-Wellcome
DRUG: Bupropion Hydrochloride Sustained Release

From: Celia Winchell, M.D.
Re: Pediatric Use of ZYBAN, Bupropion Hydrochloride Sustained Release

I do not feel that pediatric studies are indicated for Zyban. While there are patients for whom the risk of continued smoking is more worrisome than the 1/1000 risk of seizure associated with the use of this product, it is my belief that there would be few, if any, in the adolescent smoking population for whom this would be the case. Furthermore, this drug's efficacy is presumed to be mediated through CNS effects. The exact mechanism is unknown, but one might assume that it somehow alters the CNS effects of smoking. It is generally accepted that many teen smokers engage in the behavior for reasons quite apart from the CNS effects of nicotine; rather, they are influenced by "image," peer relations, and so on. Certainly there are some regular smokers among teens, even nicotine-addicted smokers. Perhaps this subpopulation would be expected to respond to Zyban as adult smokers do. However, the knowledge that at least some subset of the adolescent smoking population differs in important ways from the adult population (raising the possibility that the drug would lack efficacy) removes important weight from the "benefit" side of the risk/benefit balance. In the case of the nicotine replacement products, we have regarded the weight on the "risk" side to be small, and have encouraged pediatric studies. I do not feel this is the case with this product.

This drug is marketed for the treatment of depression as well, under the proprietary name Wellbutrin SR. I believe the sponsor has agreed to pursue pharmacokinetic studies in children under the Wellbutrin SR NDA. Therefore, should it become apparent that the drug might well be efficacious in teens, information from the Phase IV studies of Wellbutrin SR could be used to support pediatric labeling of Zyban.

TRADENAME (bupropion hydrochloride) Sustained Release Tablets

New Drug Application for Smoking Cessation

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Richard Kiernan
Vice President and Worldwide Director,
Preclinical and Clinical Compliance

21 MAR 96
Date

FDA Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville, MD 20857

Voice (301) 443-3741
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Date: 5/1/97

From: Curtis Wright, Deputy Director, HFD-170

To: NDA 20-711, Buproprion Hydrochloride SR, "Zyban"

Subject: Division Director's Approval Memo

Summary- This formulation of buproprion is already marketed as "Wellbutrin-SR", has been evaluated and has been found to be effective in smoking cessation. The safety profile in the smoking cessation indication is of acceptable risk and may be slightly better than in the already approved psychiatric indication. The product is recommended for approval.

Background and Product Description: The group leader's memorandum is complete and accurate and the reader is directed to it.

Recommendation- This is essentially a supplemental application for a new indication for Wellbutrin SR. It was filed as a new NDA and a separate product because the sponsor made an effective case that it was in the public interest to do so. The significant adverse events of concern are seizures (< 1/1000) and serious allergic reactions (<< 1/1000). There was no increase in the frequency of serious adverse reactions in the smoking cessation indication, and the rates may be lower due to a lower rate of administration of concomitant medications in this population.

The product is recommended for approval.

Curtis Wright
Acting Director,
Anesthetic, Critical Care,
& Addiction Drug Products Divisio

CC: HFD-170
NDA 20-711 ZYBAN
B McNeal
C Winchell
Div. File

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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MEMORANDUM

TO: NDA 20-711
SPONSOR: Glaxo-Wellcome
DRUG: Bupropion Hydrochloride Sustained Release

FROM: Celia Winchell, M.D.
Team Leader
Addiction Drug Products

DATE: 4/29/97

Background:
Bupropion Hydrochloride (Wellbutrin) is a marketed antidepressant which was launched in 1989. The most significant safety issue associated with Wellbutrin is a dose-dependent risk of seizures (0.4% in the doses recommended for use in treatment of depression). The manufacturer sought to develop a sustained-release formulation, both to improve compliance by offering twice daily rather than t.i.d. dosing, and in the hope of improving the safety profile.

Bupropion SR (Wellbutrin SR) was approved by HFD-120 for the antidepressant indication in October 1996. An initial non-approval action resulted from the submission of of an application which sought to change the recommended dose from 300-450 mg/day to 150-300 mg/day. An extensive safety database was developed at the lower dose range in the hope of modifying the seizure warning in the label. Although bioequivalence and safety were acceptable at a dose of 150-300 mg/day, this dose range was not felt to be efficacious for the treatment of depression. Ultimately, the approval action was based on bioequivalence and the recommended dose and seizure warning were not changed, but ample information about the 150-300 mg/day dose range was available to calculate a seizure rate for this range (0.1%, as compared to 0.4% in the range recommended for treatment of depression). Notably, 150-300 mg/day is the dose range proposed in the smoking cessation application, so information about bioequivalence and safety in this range submitted to the antidepressant NDA may be considered applicable to the smoking cessation NDA.

The first IND for the use of bupropion hydrochloride in smoking cessation was received 4/17/92. Dr. Linda Hyder Ferry submitted a proposal for a double-blind, placebo controlled 200 patient trial after having promising results in a small pilot study. Her first study (now termed "Study 401" by Glaxo Wellcome) was conducted independently, without corporate support or sponsorship and not under IND. The second study ("Study 402") was conducted with some support from the manufacturer, but was reviewed as a non-commercial IND, with attention primarily to safety and not to the adequacy of the design or analysis plan.

After promising results of Dr. Ferry's studies were presented to the manufacturer, Glaxo-Wellcome obtained an IND to study the SR formulation (then under consideration for approval as an antidepressant) in smoking cessation under IND HFD-170 staff indicated to the sponsor in a telephone conversation on 7/28/94 that Dr. Ferry's studies could not be used to support the approval of the SR formulation unless the two formulations were found to be bioequivalent.

Bioequivalence of the two formulations was accepted by HFD-120 in early 1995; accordingly, final study reports from Dr. Ferry's studies were submitted to the Glaxo-Wellcome IND.

Glaxo-Wellcome subsequently conducted two additional clinical trials using the sustained-release formulation (Studies 403 and 405). Study 403 was a dose-response trial comparing placebo vs three different doses of bupropion. Study 405 was a study that compared placebo, bupropion alone, nicotine patch alone, and the combination of the two treatments. Because Study 405 was ongoing at the time of NDA submission, the NDA, submitted 5/20/96, consisted of Studies 401, 402 and 403, with studies 402 and 403 designated as pivotal. Studies 405 and 404 (a lab study of effects on craving and withdrawal) were submitted as part of the 120-day safety update.

Because of flaws in the design, Study 401 was regarded as a supportive pilot study. The three adequate and well-controlled studies pivotal to this approval included Study 402 (WB IR 300 mg/day), Study 403 (WB SR 100, 150, and 300 mg/day), and Study 405 (WB SR 300 mg/day alone and with Habitrol Patch). The numbers of patients involved and the resultant 4-week continuous quit rates are shown below, along with a total quit rate (number abstinent/number treated with this dose) for each treatment. (Habitrol-only subjects in Study 405 are not included in this table.)

	PBO		WB SR 100 mg/day		WB SR 150 mg/day		WB SR 300 mg/day		WB IR 300 mg/day		WB SR 300 mg/day + Hab. Patch	
	N	4-wk CQR	N	4-wk CQR	N	4-wk CQR	N	4-wk CQR	N	4-wk CQR	N	4-wk CQR
Study 402	95	23.6%	- 0 -		- 0 -		- 0 -		95	36.8%	- 0 -	
Study 403	151	17.2%	153	21.6%	153	27.5%	156	35.9%	- 0 -		- 0 -	
Study 405	160	23.1%	- 0 -		- 0 -		244	49.2%	- 0 -		245	57.6%
Total	406	21.0%	153	21.6%	153	27.5%	400	44.0%	95	36.8%	245	57.6%

Taken together, these studies provide substantial evidence of the efficacy of bupropion sustained-release as an aid to smoking cessation when given at a dose of 300 mg/day in conjunction with some type of behavioral counseling. A total of 640 patients received the recommended dose (including the 95 who used the immediate-release formulation, and 245 who also used the Habitrol patch). An overall 47.6% of these acheived the 4 week continuous-quit outcome. This compares favorably to the quit rates found in controlled clinical trials of prescription nicotine replacement therapy.

No support for the efficacy of the 100 mg/day dose is present, and the evidence supporting the efficacy of 150 mg/day is not strong; thus the recommended dose for all patients should be 300 mg/day. No information is available regarding doses between 150 and 300 mg/day, and the availability of multiple tablet strengths would permit using doses in that range if 300 mg/day were poorly tolerated by an individual patient. It would be reasonable to recommend that all patients use 300 mg/day if tolerated, and that those who cannot tolerate a minimum of 150 mg/day should choose another form of smoking cessation therapy, as they are unlikely to benefit from bupropion therapy at lower doses.

The efficacy of bupropion in modifying smoker's symptoms of craving and withdrawal during a quit attempt is not as clearly delineated. Different measures of craving and withdrawal were used in the three studies. It is therefore difficult to make statements about the role of craving and withdrawal in the quit attempt using bupropion SR. A laboratory study was performed to examine this question further (Study 404) which showed small, non-specific effects on withdrawal but not on craving. A summary of findings on these measures is shown below.

	Craving	Withdrawal
Study 402	yes	yes
Study 403	no	no
Study 404	no	small, non-specific
Study 405	depends on scale	yes, for several but not all symptoms

Bupropion is associated with a risk of seizure, although none occurred in placebo-controlled trials for depression or smoking cessation. A seizure incidence of 1/1000 can be expected in the dose range used for smoking cessation, assuming precaution is taken to exclude patients with predisposition to seizure.

Bupropion is associated with a risk of allergic reactions (rash, pruritis, urticaria) that are not uncommonly cited as reasons for discontinuation of medication. Roughly 1/1000 subjects in clinical studies also experienced allergic reactions considered serious.

Other non-serious events that might prompt patients to discontinue medication include dry mouth, GI complaints, and insomnia.

Treatment-emergent hypertension has been noted in some studies to occur in more bupropion-treated patients than placebo-treated patients.

The question of Zyban's safety and efficacy for the smoking cessation indication was presented to the Drug Abuse Advisory Committee (DAAC) on 12/12/96. The committee was unanimous in its vote for approval of the drug for this indication.

The other issues addressed during the course of review are detailed below:

Nomenclature
Glaxo-Wellcome proposed to market bupropion SR for smoking cessation under a proprietary name other than Wellbutrin SR. They cited a number of reasons this would be advantageous, ranging from avoidance of stigma, to simplification of reimbursement through managed care organizations, to the facilitation of distribution of educational materials targeted to the smoking cessation population. This proposal was brought before the DAAC on 12/12/96, where the discussion focused on the risk of inadvertent dual-prescription of Wellbutrin and the as-yet-unnamed smoking cessation product, resulting in enhanced risk of seizure. The committee split evenly on the question of whether the separate name should be permitted. However, the division felt that the educational and self-help materials were a desirable feature, especially given what we have learned about the "real-world" experience of users of prescription nicotine replacement products (i.e. that they receive very little in the way of the psychosocial support the clinician is supposed to provide). Thus, we decided to permit a separate name for the product. Glaxo-Wellcome's first choice, Quitab, was rejected by the nomenclature committee as a "soundalike," and their second choice, Zyban, was accepted. The nomenclature committee noted that they felt the established name should be Bupropion, extended release, rather than Bupropion, sustained release. However, because the Wellbutrin SR (Bupropion, sustained release) is already on the market, we felt it would be confusing, if not dangerous, to assign a different established name to this product. Therefore, the proprietary name is to be Zyban, and the established name, bupropion, sustained release.

In writing the labeling and accompanying educational materials, the division focused on providing ample attention to the fact that Zyban and Wellbutrin are the same and should not be coadministered due to the dose-dependent risk of seizure. Revisions to Glaxo-Wellcome's draft labeling and ancillary materials, made by HFD-170 and DDMAC reviewers, significantly strengthened the warning and its prominence. A black-box warning was considered, but because the risk was considered, at this point, theoretical, the division decided that the addition of repetitious, prominent reminders throughout the labeling, ancillary materials, and launch advertising would be sufficient. A black-box could be considered in the future should the post-marketing experience demonstrate the present approach to be inadequate.

Role of the drug in smoking cessation treatment
The DAAC was asked to address the question of whether Zyban should be specifically labeled as a "second-line" treatment in smoking cessation. The committee agreed that nicotine replacement is probably the first-line agent for most patients, but that there were a subgroup of individuals for whom nicotine should not be used, as well as some for whom the severity of the problem and urgency of the need to quit smoking are such that a clinician should be permitted to select combination therapy for a first try without risking censure for "off-label" use.

Claims about craving, withdrawal, and weight gain
As noted above, findings related to the effects of Zyban on craving and withdrawal were variable. In negotiating the final label, we agreed to allow the sponsor to state that the drug

reduced withdrawal symptoms compared to placebo, and then to cite the specific symptoms upon which the effect was most pronounced. We allowed only a fairly "soft" claim regarding craving: "Depending on the study and the measures used, treatment with Zyban showed some evidence of reduction in craving for cigarettes or urge to smoke compared with placebo." The sponsor also did a post-hoc analysis of the weight gain experienced by the abstinent subjects in Studies 403 and 405 combined, and observed points of statistical significance. However, the magnitude of the effect (a 0.5 kg difference in weight gain between placebo and treated groups) and its duration (the difference did not persist beyond a few weeks) was so slight as to be unlikely to be clinically significant. The division encouraged the sponsor to continue to measure weight gain in future trials and indicated we would be open to including a claim regarding mitigation of weight gain if there were more substantial evidence for it.

Inclusion of information from clinical trials in the labeling:
The initial draft of the clinical trials section included information about Study 402, because it was written prior to the submission of Study 405. Ultimately, when Study 405 was reviewed and accepted as pivotal to approval, the sponsor proposed to delete information on Study 402 and replace it with information on Study 405. The division agreed that this was appropriate. While we accepted Study 402 in support of approval, it did use a different formulation from the marketed product. The availability of two studies using the marketed formulation led us to decide that it would be best to include extensive discussions of only these two studies in the label, for clarity and brevity. Claims for which support was added by 401, 402, and 404 were also included, as noted above. Negotiations of the clinical trials labeling section also included the addition of confidence intervals to the presentation of quit rates.

Educational materials for the patient
In our initial discussions with the sponsor regarding the justification for a separate proprietary name for the smoking cessation indication, the proposed patient education/behavioral materials were described as being made available upon request. Therefore, we felt at first that such materials would not be regarded as labeling, within the meaning of 21 CFR 314.50 (e)(2)(ii), but instead as promotional labeling under 21 CFR 314.81(b)(3), not requiring review by the division prior to NDA approval. However, the sponsor subsequently decided to manufacture a "starter kit," which would include a month's supply of medication, a variety of educational materials, an enrollment form for the sponsor's support program, and other items such as a pen and a magnet. Therefore, because the materials were to be distributed together with the drug, we determined that they would be reviewed as labeling. Negotiations regarding this part of the labeling, termed "ancillary materials" in our discussions with the sponsor, included revision of the "tag-line" found throughout the materials from "Now you have what it takes to quit" to "Now you have what it takes to help you quit smoking," because the former was deemed too promotional. We also asked for the inclusion of stronger and clearer messages regarding the use of additional or "prn" doses. In addition, the brochure entitled "Medication Guide" was renamed because it did not meet the DDMAC definition of a "medication guide." The text of one brochure was revised to conform with the revisions in the Patient Package Insert. Additional prominence for the coadministration and seizure warnings were added.

Title of Patient Package Insert

The sponsor proposed to place the title "Information for the Consumer" on the Patient Package Insert, because another approved product marketed by this sponsor used this language. However, DDMAC reviewers advised that, because this is a prescription product, the correct term would be "Information for the Patient." The sponsor had already printed numerous bottle labels that referred to the "Information for the Consumer," and asked that they be permitted to retain this terminology. We agreed that the launch copy could include the sponsor's language, but that subsequent printings of the bottle label and the package insert would be modified to read "Information for the Patient."

Inclusion of patent numbers in labeling

The review chemist noted some discrepancies in labeling between the approved label for Wellbutrin SR and the proposed labeling for Zyban in that there were patent numbers included in the Zyban label that were not in the Wellbutrin SR label. Upon inspection, these appeared to be for patents not entirely relevant to the product, and the chemistry team became concerned about the appropriateness of their inclusion. After discussion with the Office of New Drug Chemistry and DDMAC, the question has been referred to the Office of General Counsel. In the mean time, the patent numbers have been removed from labeling.

Harmonization of labeling with HFD-120

Although the drug product, Zyban, is identical to Wellbutrin SR, we chose not to use identical labeling. Significant points of departure from Wellbutrin SR labeling are:

We consulted with HFD-120 on our labeling, and Dr. Laughren indicated that there was no objection to the Zyban label as written.

Drug substance manufacturing process
During the process of review, the HFD-170 review chemist identified a need for inspection of the manufacturing process for bulk drug substance. Since the process was originated at a site in the U.K., there was some concern that a foreign inspection would be necessary. However, in discussions involving the sponsor, HFD-170's chemistry team, and Mark Lynch of Compliance, it was determined that adequate determination of technology transfer could be accomplished during inspection of the Greenville, NC site.

Pediatric use
The division determined that pediatric studies would not be indicated for Zyban. While there are clearly patients for whom the risk of continued smoking is more worrisome than the 1/1000 risk of seizure associated with the use of this product (or we would not approve it), we felt that there would be few, if any, in the adolescent smoking population for whom this would be the case. It is generally accepted that many teen smokers engage in the behavior for reasons quite apart from the CNS effects of nicotine; rather, they are influenced by "image," peer relations, and so on. We recognize that there are some regular smokers among teens, even nicotine-addicted smokers, and acknowledge that this subpopulation might be expected to respond to Zyban as adult smokers do. However, the knowledge that at least some subset of the adolescent smoking population differs in important ways from the adult population (raising the possibility that the drug would lack efficacy) removes important weight from the "benefit" side of the risk/benefit balance. In the case of the nicotine replacement products, we have regarded the weight on the "risk" side to be small, and have encouraged pediatric studies. We did not feel this was the case with this product. However, the sponsor has agreed to pursue pharmacokinetic studies in children under the Wellbutrin SR NDA. Therefore, should it become apparent that the drug might well be efficacious in teens, information from the Phase IV studies of Wellbutrin SR could be used to support pediatric labeling of Zyban.

Conclusions:
Recommend approval.

Celia Jaffe Winchell
Medical Team Leader
Addiction Drug Products

Medical Officer Review
NDA 20-711

Sponsor: Glaxo-Wellcome
Drug: Bupropion hydrochloride, Sustained-release
Proposed Indication: Aid to smoking cessation
Date Received by CDER: 5/20/96
Review Completed: 11/15/96
Reviewer: Celia Jaffe Winchell, M.D.

Abstract: Bupropion SR, a twice-a-day formulation of the antidepressant Wellbutrin, has recently been approved for use as an antidepressant. The sponsor has also undertaken a development program to establish its safety and efficacy as an aid to smoking cessation treatment. Four clinical trials specific to smoking cessation, as well as an extensive database encompassing the clinical development programs for both the smoking cessation and antidepressant indications were reviewed, and the recommendation is for approval.

The Drug Abuse Advisory Committee is asked to consider the safety and efficacy of bupropion SR as an aid to smoking cessation, its place in the armamentarium of smoking cessation treatment, and the acceptability of marketing it under a tradename other than "Wellbutrin SR."

The reviewer's recommendation is for approval.

1. Material Utilized in Review

1.1 Material from NDA

For this review, the study reports for Studies 401, 402, 403 and 405 were reviewed, along with electronic data for the studies. The sponsor's integrated summaries of safety and efficacy and report of post-marketing safety of Wellbutrin (immediate-release) was also reviewed.

1.2 Related Reviews

The reviews for NDA 20-358 (Burroughs Wellcome's NDA for Wellbutrin SR for the treatment of depression) from HFD-120 were consulted during the course of this review.

2. Background

2.1 Indication

The indication is "as an aid to smoking cessation treatment."
Currently available treatments for this indication include non-pharmacologic (behavioral) approaches and a variety of nicotine-replacement products. No other non-nicotine smoking cessation aid is currently FDA-approved. Nicotine replacement products are available both over-the-counter (gum and transdermal systems ("patch")) and by prescription (nasal spray, some patches not yet approved for OTC marketing); other dosage forms are in development or under FDA review.

A review of the safety of nicotine replacement has been prepared by HFD-170's Dr. E. Douglas Kramer, and is attached separately ***(Tab 9)***. Briefly, the safety record of nicotine replacement has been impressive, with very few serious adverse events, and non-serious events generally related to the route of administration (tooth and jaw problems, skin reactions, local irritation), nicotinic effects (nausea, dyspepsia), or smoking cessation itself (withdrawal, increased cough). Quit rates associated with OTC nicotine replacement, when using the generally accepted outcome measure of verified abstinence for a specified 28 day period, have been shown to be approximately 20% across a variety of studies. However, the products generally had much higher quit rates in prescription clinical trials (approximately 30-60%), generally doubling the placebo rate.

2.2 Related INDs and NDAs

IND IND IND are held by HFD-120 and pertain to the treatment of depression with Wellbutrin and Bupropion SR. The immediate-release formulation (Wellbutrin) was approved under NDA 18-644, and NDA 20-358 (Wellbutrin SR) has been approved by HFD-120, based on the establishment of bioequivalence of Buproprion SR to Bupropion.

For the smoking cessation indication, IND (investigator-initiated IND submitted by Dr. Linda Hyder Ferry) for Wellbutrin and IND commercial IND submitted by Glaxo-Wellcome)are held by HFD-170.

2.3 Administrative History

Bupropion Hydrochloride (Wellbutrin) is a marketed antidepressant which was launched in 1989. The most significant safety issue associated with Wellbutrin is a dose-dependent risk of seizures (0.4% in the doses recommended for use in treatment of depression). The manufacturer sought to develop a sustained-release formulation, both to improve compliance by offering twice daily rather than t.i.d. dosing, and in the hope of improving the safety profile.

Bupropion SR was approved by HFD-120 for the antidepressant indication in October 1996. An initial non-approval action resulted from the submission of of an application which sought to change the recommended dose from 300-450 mg/day to 150-300 mg/day. An extensive safety database was developed at the lower dose range in the hope of modifying the seizure warning in the label. Although bioequivalence and safety were acceptable at a dose of 150-300 mg/day, this dose range was not felt to be efficacious for the treatment of depression. Ultimately, the approval action was based on bioequivalence and the recommended dose and seizure warning were not changed, but ample information about the 150-300 mg/day dose range was available to calculate a seizure rate for this range (0.1%, as compared to 0.4% in the range recommended for treatment of depression). Notably, 150-300 mg/day is the dose range proposed in the smoking cessation application, so information about bioequivalence and safety in this range submitted to the antidepressant NDA may be considered applicable to the smoking cessation NDA.

The first IND for the use of bupropion hydrochloride in smoking cessation was received 4/17/92. Dr. Linda Hyder Ferry submitted a proposal for a double-blind, placebo controlled 200 patient trial after having promising results in a small pilot study. Her first study (now termed "Study 401" by Glaxo Wellcome) was conducted independently, without corporate support or sponsorship and not under IND. The second study was conducted with some support from the manufacturer, but was reviewed as a non-commercial IND, with attention primarily to safety and not to the adequacy of the design or analysis plan.

After promising results of Dr. Ferry's studies were presented to the manufacturer, Glaxo-Wellcome obtained an IND to study the SR formulation (then under consideration for approval as an antidepressant) in smoking cessation under IND HFD-170 staff indicated to the sponsor in a telephone conversation on 7/28/94 that Dr. Ferry's studies could not be used to support the approval of the SR formulation unless the two formulations were found to be bioequivalent.

Bioequivalence of the two formulations was accepted by HFD-120 in early 1995; accordingly, final study reports from Dr. Ferry's studies were submitted to the Glaxo-Wellcome IND.

2.4 Proposed Directions for Use

The most recent version of the label negotiated with the sponsor is attached separately ***(Tab 4)***. Briefly, **the indication is "as an aid to smoking cessation treatment." The intended population is all adult smokers, as no statement regarding a minimum level of smoking is present. There is no information about use in children/teens but there is guidance for geriatric use. The recommended dose and duration are 150 mg p.o. b.i.d. for 7-12 weeks.**

The recommended and maximum dose is 300 mg/day, begun as 150 mg/day x 3 days and then increased to 150 mg b.i.d. Duration is 7-12 weeks, beginning at least a week before the selected quit date (to allow levels to reach steady-state), and discontinuing after 7 weeks if the patient is still smoking. The label also states that the drug may be used in conjunction with "a nicotine transdermal system," referring the clinician to the prescribing information for each product for further information, and to the clinical trials section of the label for a description of combination therapy.

Contraindications include use in patients with seizure disorder, eating disorder, or allergy to bupropion; and concomitant administration with MAO inhibitors or other medications containing bupropion. Warnings include use in patients with predisposition to seizure due to pre-existing condition, clinical situation, or concomitant medications. The labeling provides information on reducing the risk of seizures, through limitation of maximum dose to 300 mg/day, maximum single dose 150 mg, and minimum interval between doses of 8 hours.

There is also a warning regarding pre-clinical evidence of hepatocellular injury from the drug.

Precautionary information is provided regarding the incidence of insomnia in clinical trials, and, in keeping with the approved label for the anti-depressant indication, information is provided regarding neuropsychiatric symptoms and the potential for activation of mania. Allergic reactions are also mentioned as a precaution. Caution is advised in administering the drug to those with CHF, renal impairment or hepatic insufficiency. The possibility of interactions with other drugs which affect cytochrome $P_{450}IIB_6$ metabolism is mentioned, as well as precautions regarding coadministration with MAO inhibitors or levodopa. Other drugs for which caution is advised prior to coadministration include carbamazepine, phenobarbital, phenytoin, and cimetidine, as well as any drug which lowers seizure threshold. Information is also provided regarding the effects on smoking cessation *per se* on metabolism of various drugs.

The drug is classified as belonging to pregnancy category B. However, it is recommended that pregnant smokers attempt cessation through non-pharmacologic approaches initially. It is secreted in breast milk, and there is deemed to be a risk of adverse reactions in nursing infants; thus the options recommended include discontinuing breast feeding or discontinuing the medication.

There is little information about pediatric use; the sponsor did not feel the database was sufficient to make statements about the use of this drug in children, although it has been tested in approximately 100 children in clinical trials for use in treatment of Attention Deficit Disorder. The sponsor has a Phase IV committment (from approval letter HFD-120) to study the use of the medication in children and adolescents with depression, beginning with pharmacokinetid studies in this population.

Information about use in the elderly suggests that the experience with older patients is similar to the overall population.

The proposed labeling describes the information available for overdose with reference to the experience involving the immediate release formulation. The drug dependence section notes a low abuse potential, although bupropion was self-administered in animal models, resembled stimulants in drug-discrimination paradigms, and was liked by human subjects when administered to individuals experienced with drugs of abuse when administered at doses above that recommended for this indication. Because of these findings, which suggest that supratherapeutic doses may be perceived as rewarding, but have potential to induce seizures, the clinician is cautioned to bear in mind the patient's substance abuse history when selecting a smoking cessation treatment.

2.5 Foreign Marketing

Neither bupropion nor bupropion SR has been marketed outside the United States. Applications to market the immediate release formulation were submitted in Canada and the UK, but were withdrawn without prejudice after deficiencies were identified.

2.6 Special Topic: Nomenclature

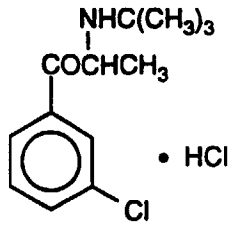
Glaxo Wellcome has developed Bupropion SR for two separate indications: smoking cessation and depression. They the are marketing the anti-depressant under the tradename Wellbutrin SR, and would like to market the smoking cessation aid under a different tradename. The main issue of concern is that bupropion has a well-known, dose-dependent risk of precipitating seizures, estimated at 0.1% for doses up to 300 mg/day (as proposed for smoking cessation), at 0.4% for doses 300-450 mg/day (recommended range for antidepressant), with a significant increase in rate for higher doses which could easily be obtained by a patient combining the recommended dose for smoking cessation with the recommended dose for depression. The use of two different names increases the likelihood of inadvertent "double dosing," either by a single practitioner who did not recognize the two medications to be identical, or by two practitioners, with the patient failing to recognize the duplication and draw the physician's attention to it.

The sponsors cite three main reasons for their proposal for a distinct tradename for the smoking cessation product. First, they mention facilitation of the distribution of educational materials to be used in conjunction with the product for smoking cessation. The sponsor would like to package self-help materials for smoking cessation with the medication, and have a patient package insert geared to this indication. Second, they fear that patients will resist using the medication because it is known as an antidepressant, or that they may face adverse consequences as a result of others learning of and misinterpreting their use of this medication. Through using a distinct tradename, patients would avoid the stigma faced by users of anti-depressants. Third, the sponsor reports that having one tradename for the two very different indications would complicate reimbursement procedures through managed care organizations, and would result in patients failing to receive reimbursement for bupropion even when their policy covers smoking cessation aids.

A review of the sponsor's request, and the risks, benefits, and regulatory options is included separately ***(Tab 13)***. The reviewer's conclusion is that adequate labeling could be developed to manage the risk, and that future bupropion products with different tradenames (from different manufacturers) are likely to be inevitable; thus the recommendation is that the request be granted contingent upon agreement on adequate labeling.

3. Chemistry

The chemistry of the product has been reviewed separately, both in HFD-120 and by HFD-170's review chemist, Pramoda Maturu ***(Tab 12)***. Briefly, WELLBUTRIN® SR is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride (HCl) powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



This product is supplied for oral administration as 50-mg (white), 100-mg (blue), and 150-mg (purple), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion HCl and the inactive ingredients carnauba wax, cysteine hydrochloride, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide and is printed with edible

black ink. In addition, the 100-mg tablet contains FD&C Blue No. 1 Lake and polysorbate 80, and the 150-mg tablet contains FD&C Blue No. 2 Lake, FD&C Red No. 40 Lake, and polysorbate 80.

4. Animal Pharmacology

The pre-clinical pharmacology has been reviewed in HFD-120, as well as by HFD-170's review pharmacologist, Belinda Hayes.

Briefly, bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase.

Acute toxicity was tested in rats and mice. The LD_{50} in mice was 544 mg/kg for males and 636 mg/kg for females. In rats, the LD_{50} was 607 mg/kg for males and 482 mg/kg for females. Signs of acute toxicity included labored breathing, salivation, arched back, pstosis, ataxia, and convulsions. A multi-dose toxicity study of sustained-release bupropion in rats involved three-month administration of both degraded and undegraded compound. Findings included dose-related salivation and increases in liver and thyroid weights due to reversible microsomal enzyme induction.

Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg per day, respectively. These doses are approximately ten and two times the maximum recommended human dose (MRHD), respectively, on a mg/m^2 basis. In the rat study, there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg per day (approximately three to ten times the MRHD on a mg/m^2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (two to three times control mutation rate) in two of five strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in one of three in vivo rat bone marrow cytogenic studies.

Reproduction studies have been performed at doses up to 300 mg/kg (fertility study) or 450 mg/kg (teratology studies) in rats (approximately fourteen times the MRHD on a mg/m^2 basis) and at doses up to 150 mg/kg in rabbits (approximately ten times the MRHD on a mg/m^2 basis) and have revealed no evidence of impaired fertility or harm to the fetus due to bupropion

5. Human Pharmacokinetics Considerations

The pharmacokinetics of bupropion SR have been reviewed separately, both in HFD-120 and by HFD-170's biopharmaceutics reviewer, Peter Lockwood ***(Tab 11)***. Briefly, Bupropion follows biphasic pharmacokinetics best described by a 2 compartment model. The terminal phase has a half-life of about 20 hours (approximately 20% CV) while the distribution phase has a half-life of 3-4 hours. Wellbutrin has not been administered intravenously to humans, therefore the absolute bioavailability of Wellbutrin tablets in man has not been determined. Studies in rat and dog indicated the bioavailability ranged from %. In vitro tests show that bupropion is approximately 80% bound to human plasma proteins at plasma concentrations up to 200 µg/mL.

Bupropion has three active metabolites; 306U73 (hydroxybupropion), and the aminoalcohol isomers 494U73 (threohydrobupropion) and 17U67 (erythrohydrobupropion). The potency and toxicity of the metabolites relative to bupropion have not been fully characterized, however it has been demonstrated in mice that hydroxybupropion is comparable in potency to bupropion while the other metabolites are one tenth to one half as potent. This may be of clinical importance because the plasma concentrations of the metabolites are higher than those of bupropion. In vitro and in vivo findings suggest that CYP2B6 is the principal isozyme involved in the formation of hydroxybupropion while P450's are not involved in the formation of threohydrobupropion.

The total clearance (CL/F) estimated estimated from a single dose (150mg CR) study is 135L/Hr (20%CV). The mean elimination half-life of bupropion estimated from a series of studies is approximately 20 hours (CV up to 40%). Estimates of the half-lives of the metabolites determined from a multiple dose study were 20 hrs (CV25%) for hydroxybupropion (306U73), 37 hours (35%CV) for threohydrobupropion and 33 hrs (30%CV) for erythrohydrobupropion. Steady-state plasma concentrations of bupropion are reached within 5 days and 8 days for the metabolites.

Following oral administration of bupropion SR Tablets to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. The mean Cmax ranges from 50-65ng/ml following a 100mg CR dose.

The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion SR, there was no statistically significant difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its major metabolites between smokers and nonsmokers.

6. Clinical Trials

There were four clinical trial reports submitted in support of this NDA. Full reviews of each trial are included separately *(Tab 7)*. Summaries of the reviews are below.

6.1 Study 401: A Single Center Evaluation of Wellbutrin (bupropion hydrochloride) Versus Placebo as an Aid to Smoking Cessation

This was a single-center, parallel, randomized, double-blind, placebo-controlled trial involving 52 male outpatients who were heavily-dependent, chronic cigarette smokers. This pilot study was conducted by the Principal Investigator of Study 402. The medication used in this study was the immediate release formulation of Wellbutrin. Twelve of 27 Wellbutrin-treated patients and one of 25 Placebo-treated patients successfully quit for a period of 4 weeks during the treatment phase. All but one of the abstinent Wellbutrin patients maintained abstinence through 12 months of follow-up. Although the results were encouraging, flaws in randomization render this study supportive, but not substantial evidence of efficacy. However, it is a helpful pilot study, with findings indicating that Wellbutrin 300 mg/day is effective as an aid to smoking cessation when used in conjunction with group counseling sessions, and that it is relatively well-tolerated, with few serious adverse events and few premature discontinuations related to non-serious events. Drug-related events appear to include sleep disturbance, dry mouth, tremor, and anxiety.

6.2 Study 402: Evaluation of Wellbutrin (bupropion hydrochloride) Versus Placebo as an Aid to Smoking Cessation

This was a two-center, parallel, randomized, double-blind, placebo-controlled trial involving 190 male and female chronic, heavy (≥20 cigarettes/day) cigarette smokers. The study was conducted under an individual investigator IND and used the immediate-release formulation of Wellbutrin. Although generally well-conducted, a variety of protocol violations allow a range of interpretation of the efficacy outcome. The *a priori* primary efficacy measure was abstinence from smoking during any 4-week period of the Treatment Phase (Day 1 through Day 56). Quit rates are shown below:

Four-Week Quit Rates Based on Various Classifications of Patients

	Placebo		Wellbutrin				
	N	%	N	%	p-value	Odds Ratio	95% C.I.
Self-report	25	26.3	41	43.2	0.02	2.13	1.16 - 3.91
Cotinine Confirmed	22	23.2	35	36.8	0.04	1.94	1.03 - 3.64
"Worst Case"	15	15.8	27	28.4	0.04	2.12	1.04-4.31

(Table prepared by medical and statistical reviewers from sponsor's data)

Thus, even in a worst-case scenario analysis, the active drug shows improvements over the placebo quit-rate. This study demonstrates that motivated, non-depressed heavy smokers treated with Wellbutrin, 100 mg t.i.d., in conjunction with bi-weekly, hour-long group smoking cessation achieve abstinence lasting at least 28 days at a rate superior to those treated with placebo. This finding persists through 6 months of follow-up. The sample was primarily comprised of middle-aged white males, and extrapolation to other populations would need to be done cautiously in the absence of confirmation of these findings in a broader population.

Wellbutrin showed significant effects on withdrawal symptoms as measured by a weekly withdrawal scale. The effect was most notable on the subscales measuring nicotine craving and anger, but significant effects were also found on subscales measuring anxiety, frustration, and difficulty concentrating, as well as on the composite score. Two additional measures of craving also showed significance at various time-points, confirming the finding of significant differences on the nicotine craving subscale of the withdrawal measure. These findings were not confirmed in Study 403.

No patients died during the treatment phase of the study. One patient randomized to placebo died after the completion of the treatment phase, and two placebo-group patients died following discontinuation from the study. There were no other serious adverse events reported during the conduct of the study. There were no seizures reported.

Non-serious AE's were collected using a checklist. Among patients receiving Wellbutrin, the most commonly reported non-serious AE's (≥10% of the group) were dry mouth, headache, sleep disorder (Costart term for checklist item "sleep disturbance"), and constipation. For the placebo group, there were no AE's reported by more than 7% of the group. There were six AE's for which the rate of occurrence in any of the WB SR treatment groups differed from placebo by more than 5%. These included dry mouth, sleep disorder, headache, constipation, diarrhea, and hypertension (includes increases in blood pressure).

This study serves as substantial evidence of the efficacy of bupropion as an aid to smoking cessation when used in motivated smokers in conjunction with a program of group therapy.

6.3 Study 403: A Multicenter Dose Response Evaluation of Wellbutrin (bupropion hydrochloride) Sustained Release Versus Placebo as an Aid to Smoking Cessation

This was a parallel, randomized, multicenter, double-blind, placebo-controlled trial involving 615 male and female chronic cigarette smokers. The objective of this trial was to compare the safety and efficacy of three doses of sustained-release bupropion and placebo as aids to smoking cessation in chronic cigarette smokers when used in conjunction with brief, individual counseling.

The *a priori* primary efficacy measure was abstinence from smoking during a specified 4-week period of the Treatment Phase (Weeks 4 through 7). Safety assessments included vital signs, weight, and an adverse experience probe.

Abstinence was defined as self-report of smoking zero cigarettes, confirmed by exhaled CO. However, some subjects who missed visits were defined as abstinent if confirmatory CO was available before and after the missing visit, and some subjects who used certain medications in violation of protocol were also included as abstinent if they otherwise met criteria. Quit rates based on the sponsor's vs. a "worst-case," strictest definition of abstinence are shown below.

	Comparison of CQR at Three Time Points Using Sponsor's vs Strictest Definition of Abstinence															
	PBO (N=151)				WB SR 100 (N=153)				WB SR 150 (N=153)				WB SR 300 (N=156)			
Time Point	sponsor		"worst-case"		sponsor		"worst-case"		sponsor		"worst-case"		sponsor		"worst-case"	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
4 weeks	26	17.22	23	15.23	33	21.57	30	19.61	42	27.45	36	23.53	56	35.90	47	30.13
6 months	17	11.26	17	11.26	25	16.34	24	15.69	28	18.30	28	18.30	30	19.23	28	17.95
12 months	15	9.93	15	9.93	20	13.07	18	11.76	23	15.03	21	13.73	21	13.46	19	12.18

(Table prepared by reviewer from sponsor's data)

The quit rates for the medication-treated groups remain superior to placebo in an essentially dose-dependent fashion throughout the follow-up period. A consideration of the appropriateness of including each subject who is excluded in the "worst-case" analysis reveals that it is reasonable to include most of them, and that the sponsor's quit rates can be accepted.

This study demonstrates that motivated smokers treated with bupropion SR for at least seven days prior to a quit attempt supported by brief counseling achieve abstinence at a rate superior to those treated with placebo. This finding is statistically significant through 8 weeks of follow-up in subjects treated with either 150 mg/day or 300 mg/day. The statistical significance persists through 6 months of follow-up for subjects treated with 300 mg/day.

No significant effect of bupropion on withdrawal symptoms as measured by a weekly withdrawal scale was identified.

No consistent pattern was identified to suggest that depression history had an effect on the outcome for individual subjects.

No patients died during the treatment phase of the study. However, one subject died of pulmonary edema two weeks after completing the 49-day treatment phase on WB SR 300. The patient had severe, pre-existing medical problems, and it seems plausible to classify this event as unrelated to study drug.

Two non-fatal serious adverse events occurred during the treatment phase of the study. One subject experienced an episode of uncharacteristic "**uncontrollable rage**" during a traffic incident. The event is judged to be possibly attributable to study drug

One subject experienced an **anaphylactic reaction** (dyspnea, swelling, and petechiae) during the treatment phase of the study. It would seem unlikely that the reaction, which occurred the day after stopping WB SR, would be caused by the study drug, but anaphylaxis and allergic reactions (rash, urticaria, pruritis) have been reported in association with bupropion and bupropion SR; therefore the event can be considered possibly related to study drug.

There were also two SAE's during follow-up involving subjects randomized to placebo: A 47 year-old male subject experienced a myocardial infarction and a 71 year-old white female subject contracted pneumonia.

There were no seizures during the study.

Bupropion SR appeared to be reasonably well-tolerated.Non-serious adverse events which appear to be related to study drug include dry mouth, insomnia, and allergic phenomenon. The most common reasons for early termination due to adverse events (includes placebo patients) were headache, allergic phenomenon, GI symptoms, tremor, and emotional symptoms (hostility, lability, and depression).

Bupropion SR demonstrated no significant effects on vital signs or weight.

This study serves as substantial evidence of the efficacy of bupropion SR as an aid to smoking cessation when used in motivated smokers in conjunction with a program of brief counseling. The most effective dose tested is 300 mg/day, which should be the recommended dose.

6.4 Study 405: A Multicenter Evaluation of Wellbutrin (Bupropion Hydrochloride) Sustained Release, Habitrol (Nicotine Transdermal System), and Combination Wellbutrin Sustained Release/Habitrol Treatment versus Placebo as Aids to Smoking Cessation

This was a parallel, randomized, multicenter, double-blind, double-dummy placebo-controlled trial involving 893 male and female chronic cigarette smokers. The objective of this trial was to evaluate the efficacy and safety of WELLBUTRIN SR (WB SR) 300 mg/day compared to placebo (PBO) as an aid to smoking cessation in chronic cigarette smokers when used in conjunction with brief, individual counseling, and to evaluate the efficacy and safety of combination WB SR/HABITROL (WB SR/HAB) treatment compared to WB SR or HABITROL (HAB) alone as aids to smoking cessation in chronic cigarette smokers when used in conjunction with brief, individual counseling. A secondary objective of this study was to compare the efficacy and safety of WB SR and HAB treatment in chronic cigarette smokers.

The *a priori* primary efficacy measure was abstinence from smoking during a specified 4-week period of the Treatment Phase (Weeks 4 through 7). Safety assessments included vital signs, weight, and an adverse experience probe.

Preliminary results for the treatment phase of the study were reported by the sponsor. A review of the determinations of evaluability for subjects and the classifications of subjects as smokers or abstinent revealed that the sponsor's figures are acceptable. The continuous quit rates for Weeks 4 through 7 are shown below.

	Treatment Group			
	PBO	HAB	WB SR	WB SR/HAB
4- week CQR*	23.1%	36.1%	49.2%	57.6%
p-value vs placebo	n/a	<0.01	<0.001	<0.001
p-value vs HAB		n/a	<0.01	<0.001
p-value vs WB SR			n/a	0.06

*Continuous Quit Rate

In this study, bupropion SR appeared to reduce withdrawal symptoms and to reduce the rate of early relapse in those who made a quit attempt, as compared to treatment with placebo or with transdermal nicotine alone.

There were three deaths during the study. All three occurred during the follow-up phase, involved patients who had been randomized to receive Habitrol only, and were considered not reasonably attributable to study drug. These included a 67 year-old white female who experienced a fatal myocardial infarction approximately three months after completing the Treatment and Taper phases; a 68 year-old white female who died of a pulmonary embolus approximately 4.5 months after discontinuing study medication; and a 52 year-old white male who sustained a fatal head injury in an accidental fall approximately 6 months after his last dose of study medication.

There were ten non-fatal serious adverse events, five of which occurred during the Treatment and Taper Phases and five during Follow-up. Three events were judged to be reasonably attributable to study drug, and all involved anaphylactoid reactions in patients receiving active bupropion SR.

A 46-year-old white female, randomized to receive WB SR, required emergency room treatment of an **allergic reaction** characterized by rash, pruritus, and dyspnea. She received subcutaneous epinephrine and Benadryl and was discharged the same morning on oral antihistamines. Study medication was discontinued at that time. The reaction was judged to be reasonably attributable to study drug.

A 36-year-old white female, randomized to receive WB SR, experienced **pruritus, hives, diffuse rash**, and lower **chest tightness on deep inspiration** requiring emergency room treatment with subcutaneous epinephrine, and intravenous saline and Solu-Medrol. The ER diagnosis was **erythema multiforme**. She was discharged later that day on oral prednisone. The event was judged to be reasonably attributable to study drug.

A 34-year-old white female, randomized to receive WB SR/HAB, developed pruritis and hives requiring treatment with prednisone, cimetidine, and Benadryl at an urgent care facility. Subsequently she noted swelling in her hands and knees and was treated in an emergency room with with Solu-Medrol, Susphrine, Benadryl, and albuterol, receiving a diagnosis of **acute drug hypersensitivity reaction**. She subsequently presented to her physician with pruritus and extensive urticaria. She was prescribed Atarax, which alleviated her symptoms. These events were judged to be reasonably attributable to study drug.

Four other serious adverse events occurring in patients treated with bupropion SR were not reasonably attributable to study medication. These included a 45 year-old white female (WB SR) who was hospitalized for evaluation of chest pain two days after completing the Taper Phase; a 58 year-old white female (WB SR/HAB) experienced leg pain approximately 4.5 months after discontinuing study medication and received a diagnosis of "borderline lupus" from her personal MD; a 59 year-old white female (WB SR/ HAB) was hospitalized overnight for rheumatoid arthritis approximately 7 months after her last dose of study medication; and a 46 year-old white male (WB SR) was hospitalized for evaluation of chest pain on day 4 of the study and was diagnosed with gastric reflux.

The remainder of the serious events occurred in subjects randomized to receive either placebo or Habitrol alone.

Non-serious AE's appearing to be related to bupropion SR included insomnia, dry mouth, nausea, and constipation.

It was observed that the combination treatment was associated with a higher rate of treatment-emergent reports of hypertension than the other treatments.

This study serves as substantial evidence of the efficacy of bupropion SR as an aid to smoking cessation when used in motivated smokers in conjunction with a program of brief counseling. The combination of bupropion SR and transdermal nicotine is also shown to be superior to placebo and the risk of the combination appears to be similar to the risk of bupropion alone, although monitoring for treatment-emergent hypertension would be prudent.

7. Integrated Review of Efficacy

An integrated review of the efficacy of bupropion SR for smoking cessation, prepared by the sponsor and reviewed for accuracy by FDA, is provided separately.

Briefly, the three adequate and well-controlled studies pivotal to this approval included Study 402 (WB IR 300 mg/day), Study 403 (WB SR 100, 150, and 300 mg/day), and Study 405 (WB SR 300 mg/day alone and with Habitrol Patch). The numbers of patients involved and the resultant 4-week continuous quit rates are shown below, along with a total quit rate (number abstinent/number treated with this dose) for each treatment. (Habitrol-only subjects in Study 405 are not included in this table.)

	PBO		WB SR 100 mg/day		WB SR 150 mg/day		WB SR 300 mg/day		WB IR 300 mg/day		WB SR 300 mg/day plus Habitrol Patch	
	N	4-wk CQR	N	4-wk CQR	N	4-wk CQR	N	4-wk CQR	N	4-wk CQR	N	4-wk CQR
Study 402	95	23.6%	- 0 -		- 0 -		- 0 -		95	36.8%	- 0 -	
Study 403	151	17.2%	153	21.6%	153	27.5%	156	35.9%	- 0 -		- 0 -	
Study 405	160	23.1%	- 0 -		- 0 -		244	49.2%	- 0 -		245	57.6%
Total	406	21.0%	153	21.6%	153	27.5%	400	44.0%	95	36.8%	245	57.6%

(Table prepared by reviewer from sponsor's data)

Taken together, these studies provide substantial evidence of the efficacy of bupropion sustained-release as an aid to smoking cessation when given at a dose of 300 mg/day in conjunction with some type of behavioral counseling. A total of 640 patients received the recommended dose (including the 95 who used the immediate-release formulation, and 245 who also used the Habitrol patch). An overall 47.6% of these acheived the 4 week continuous-quit outcome. This compares favorably to the quit rates found in controlled clinical trials of prescription nicotine replacement therapy.

No support for the efficacy of the 100 mg/day dose is present, and the evidence supporting the efficacy of 150 mg/day is not strong; thus the recommended dose for all patients should be 300 mg/day. No information is available regarding doses between 150 and 300 mg/day, and the availability of multiple tablet strengths would permit using doses in that range if 300 mg/day were poorly tolerated by an individual patient. It would be reasonable to recommend that all patients use 300 mg/day if tolerated, and that those who cannot tolerate a minimum of 150 mg/day should choose another form of smoking cessation therapy, as they are unlikely to benefit from bupropion therapy at lower doses.

The efficacy of bupropion in modifying smoker's symptoms of craving and withdrawal during a quit attempt is not as clearly delineated. Different measures of craving and withdrawal were used in the three studies. It is therefore difficult to make statements about the role of craving and withdrawal in the quit attempt using bupropion SR. A laboratory study was performed to examine this question further (Study 404) which showed small, non-specific effects on withdrawal but not on craving ***(Tab 8)***.

	Craving	**Withdrawal**
Study 402	**yes**	**yes**
Study 403	**no**	**no**
Study 404	**yes**	**yes**
Study 405	**depends on scale**	**possible**

8. Integrated Review of Safety

Because this drug has been approved for marketing as an anti-depressant, to some extent one might view this application as an efficacy supplement. However, one must make a separate assessment of risk and benefit for each indication, as it may be the case that the morbidity and mortality associated with a given condition, or the safety and efficacy of currently-available treatments for that condition, would render the risks associated with the proposed treatment to be more or less acceptable.

The sponsor has prepared an integrated review of the safety of bupropion SR, incorporating the experience with the drug as an anti-depressant as well as its record in the clinical trials for smoking cessation. It has been reviewed for accuracy by the FDA reviewer, and is attached separately. The brief summary below is based primarily on the sponsor's briefing document, ISS submitted to the NDA, materials from the HFD-120 review, and on primary review of the clinical studies for smoking cessation.

8.1 Deaths

There were nine deaths reported in during the conduct of the smoking cessation studies. All occurred during the one-year follow-up period after study medication had been discontinued. Only two involved patients who had received bupropion or bupropion SR. Causes of death included pulmonary edema in one case and hypotension following CABG in a second. Four deaths were reported in patients who received placebo (two cases of myocardial infarction, one case of emphysema, and one of complications following leg amputation in a diabetic), and three in patients who had received Habitrol (myocardial infarction, pulmonary embolus, and accidental injury).

There were no deaths in the pooled safety database in the depression trials (Study 203, Study 204 and Study 212, N = 987). Six deaths occurred in the large open-label trial (Study 208, N = 3100): three due to suicide, one due to homicide, and two due to cardiac illness (not considered related to study drug).

8.2 Dropouts

Because premature discontinuation in smoking cessation trials is frequently due to lack of efficacy rather than to lack of tolerability of the medication, the overall rate of dropout is often high while the rate of dropout due to adverse events is low. This is the case in the clinical trials reported in this application. Discontinuation due to adverse events occurred in 6 - 13% of bupropion treated patients vs 4 - 5% of placebo-treated patients. No clear pattern was noted. In the depression studies, overall rate of discontinuation for adverse events was 7% in the bupropion-treated group in placebo-controlled trials, vs 4% in the placebo group. In the open-label safety study, 11% discontinued prematurely due to an adverse event.

8.3 Other serious adverse events

A total of 37 SAE's have been reported during the smoking cessation studies as of 10/7/96. These include the nine deaths discussed above and 28 non-fatal SAE's. Seventeen of these involved patients who were receiving bupropion or bupropion SR. For eight patients, the treatment assignment is unknown because they are in an ongoing study and the blind has not been broken. Only the following were considered related (possibly attributable or reasonably attributable) to study drug.

Event	Subject	Treatment	Action
Uncontrollable Rage	25 yo WM, Study 403	WB SR	tx d/c'd
Anaphylaxis	66 yo WF, Study 403	WB SR	tx d/c'd
Allergic Reaction	46 yo WF, Study 405	WB SR	tx d/c'd
Disseminated Rash	36 yo WF, Study 405	WB SR	tx d/c'd
Hypersensitivity Drug Reaction	34 yo WF, Study 405	WB SR/HAB	tx d/c'd

The events occurring in studies 403 and 405 are more fully described in the study reviews.

Serious adverse events in the depression studies included nine in the placebo-controlled studies (Six in WB SR-treated patients (N = 987) and three in placebo treated patients (N = 385)) and 54 in the safety surveillance study (N = 3100). None of the events in the placebo-controlled studies were judged to be reasonably attributable to study drug. Only four of the events in the safety study were judged to be possibly attributable. These included two cases of panic attack, one case of somnolence, and one of facial edema. There was also an episode of urticaria that was attributed to pinpricks during a neurologic exam, and judged not reasonably attributable to study drug. However, the treatment required included such systemic interventions as steroids and bronchodilators, suggesting that a relationship to study drug should not be ruled out.

8.3.1 Serious Allergic Reactions

A total of four serious allergic reactions in the smoking cessation studies and two in the depression safety study were noted. In a large, open-label safety study of the IR formulation, there was one additional patient who required emergency room treatment with epinephrine and steroids for hives, and a patient who required steroids for rash. The incidence of these events calculated from these observations would be 2/1000 in the smoking cessation studies, 5/10,000 in the safety study of the SR formulation and 1/1000 in the safety study of the IR formulation. The overall rate would be 1/1000. There are also two MedWatch SRS reports of anaphylaxis related to the IR formulation, and six reports of serious anaphylactoid reactions (includes angioedema, urticaria, hypotension, shock, apnea, asthma, dyspnea, edema larynx, hypoventilation, respiratory distress, laryngismus, stridor). By comparison, there have been 385 reports of seizure.

8.3.2 Seizures

Seizures are the best-known risk associated with the use of bupropion. To some extent, the concern over seizures precipitated by bupropion was drawn primarily from a single study, in which four subjects in a small (N = 55) trial to evaluate bupropion as a treatment for bulimia experienced unexplained seizures. This occurred between the approval of the drug and widespread marketing, and resulted in withdrawal from the market in order to pursue a large-scale safety study to establish the incidence of seizures. This 3277 patient study yielded the information presently contained in the Wellbutrin and Wellbutrin SR labels: the incidence of seizures is 4/1000 in doses of 300-450/day, and rises dramatically as dosing increases above 450 mg/day. A large-scale (N = 3100) safety study of the SR formulation at 150-300 mg/day established a 1/1000 rate at this dose; there is no reason to expect the experience with this dose in a smoking cessation population would be different, assuming that similar selection criteria are used. No seizures were observed in the smoking cessation studies (N = 1946), but it must be noted that substance abuse/dependence (other than nicotine), medical or psychiatric illness, and use of concomitant psychoactive medications were exclusion criteria. Thus, one can confidently extrapolate the seizure rate to generally healthy smokers, but the rate of seizure might be expected to be higher in polysubstance abusers and those on multiple medications. Clinical studies in approximately 100 cocaine abusers and 40 alcoholics have been conducted, and no seizures occurred in these groups; however this drug would nevertheless not be appropriate in settings such as drug rehab, psychiatric units, and jails where forced abstinence from cigarette smoking might suggest an opportunity for the clinician to encourage a quit

attempt. Nicotine gum has been used in such settings, and it should be emphasized that this patient population is not the target group for bupropion SR.

There have been 385 SRS reports of seizure from launch of Wellbutrin through 5/31/95. Seizures reported in the SRS have only rarely been associated with a fatal outcome. The five seizure-related deaths were all associated with underlying medical conditions.

8.4 Non-Serious Adverse Events
Adverse event incidence tables are provided in the sponsor's briefing document (q.v.), and in the reviews of the individual studies ***(Tab 7)***.

Briefly, dry mouth and insomnia appeared to be related to bupropion in all three clinical trials for smoking cessation. Constipation was also noted in two trials, and allergic phenomena (pruritis, rash, urticaria) also appeared to be related in Study 403, while the relationship may have been obscured in Study 405 by the use of active and placebo patches in all subjects. There was some indication, however, that in each pair (PBO vs WB SR, using dummy patches, and HAB vs WB SR/HAB, using active patches), the incidence of allergic reactions including application site reaction was higher in the subjects on active WB SR than those on placebo tablets.

8.5 Vital signs
The number of patients meeting criteria for hypertension has been higher in bupropion-treated than in placebo-treated patients in several studies, although clinically significant differences have not been noted. However, particularly in the case of the combination of bupropion with nicotine replacement, monitoring for treatment-emergent hypertension would seem prudent.

8.6 Withdrawal Phenomena/Abuse Potential
The clinical trials were conducted using abrupt discontinuation of medication at the end of treatment and reports of withdrawal phenomena were not observed. There have been some SRS reports of withdrawal phenomena associated with Wellbutrin, but this is not uncommon with antidepressants not felt to have abuse potential (e.g. Paxil). In general, however, bupropion is felt to have a low abuse potential based on results of testing, clinical trials, and post-marketing experience.

8.7 Overdose experience
There has been extensive experience with overdosages of the immediate-release formulation of bupropion. Thirteen overdoses occurred during clinical trials in depressed patients. Twelve patients ingested 850 to 4,200 mg and recovered without significant sequelae. Another patient who ingested 9,000 mg of the immediate-release formulation of bupropion and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

Since introduction, overdoses of up to 17,500 mg of the immediate-release formulation of bupropion have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of the immediate-release formulation of bupropion alone included hallucinations, loss of consciousness, and sinus tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when the immediate-release formulation of bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of the immediate-release formulation of bupropion alone have been reported rarely in patients ingesting massive doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

8.8 Summary of key adverse findings
Bupropion is associated with a risk of seizure, although none occurred in placebo-controlled trials for depression or smoking cessation. A seizure incidence of 1/1000 can be expected in the dose range used for smoking cessation, assuming precaution is taken to exclude patients with predisposition to seizure.

Bupropion is associated with a risk of allergic reactions (rash, pruritis, urticaria) that are not uncommonly cited as reasons for discontinuation of medication. Roughly 1/1000 subjects in clinical studies also experienced allergic reactions considered serious.

Other non-serious events that might prompt patients to discontinue medication include dry mouth, GI complaints, and insomnia.

Treatment-emergent hypertension has been noted in some studies to occur in more bupropion-treated patients than placebo-treated patients.

9. Labeling review
The sponsor's original proposed labeling and the latest version agreed upon are attached ***(Tab 4)***. Significant changes from the original version include the deletion of references to Study 401, a more prominent warning about combining "Tradename" with Bupropion, Wellbutrin, or Wellbutrin SR, clarifications in dosing instructions, and changes in the formats of the adverse events sections. The wording regarding abuse liability has also been strengthened and revisions of the pharmacokinetics section to improve readability have been made.

10. Conclusions
The efficacy of bupropion SR, 300 mg/day in two divided doses, when administered in conjunction with some type of behavioral support, has been demonstrated in two clinical trials. A third positive clinical trial using the same dose but the immediate-release formulation provides further support for the conclusion of efficacy, as the two formulations are regarded as bioequivalent. Weak evidence exists to support the efficacy of 150 mg/day, but no support for lower doses is established. The product is associated with a dose-dependent risk of seizures, but the rate for doses in the range recommended for this indication is 0.1%, and careful patient selection, with somewhat greater constraints than those placed on the clinician using this product to treat depression, could further reduce the risk. The drug has been combined with nicotine replacement in one study with the only adverse outcome noted being a slightly higher incidence of hypertension, the immediate release formulation has been used by smokers, and there is no pharmacologic basis for predicting adverse interactions between this product and nicotine. It seems reasonable to conclude that this drug can be safely combined with a nicotine transdermal system, as described in the proposed labeling.

Few serious adverse events occurred during testing. No seizures occurred. There were four incidents of anaphylactoid reactions in which emergency-room treatment was required. The labeling has included a warning regarding these events.

The proposal to market this drug under a new tradename, while simultaneously marketing it as Wellbutrin SR for depression, could increase the likelihood of inadvertent "double-dosing" and a greater risk of seizure. Careful labeling will be needed to address this possibility.

Consideration of the place of this drug in the armamentarium of smoking cessation treatments will include the relative risk of treatment with bupropion SR as compared to treatment with nicotine replacement, as well as the relative efficacy of the treatments.

11. Recommendations
Approval is recommended.

Celia Jaffé Winchell, M.D.
Medical Officer
11/15/96

Curtis Wright, M.D., M.P.H.
Peer Reviewer
11/15/96

Archival: NDA 20-711
cc:
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HFD-170/P. Maturu
HFD-170/C. Q. Li
HFD-170/ Division File

MEDICAL OFFICER COMMENTS

NDA 20-711
SPONSOR: Glaxo-Wellcome
DRUG: Bupropion SR
TYPE OF SUBMISSION: Advisory Committee Briefing Document including Integrated Summaries of Safety and Efficacy
MEDICAL OFFICER: Celia Winchell
DATE RECEIVED BY CDER: 11/12/96
DATE REVIEW COMPLETED: 11/15/96

A briefing document including an integrated summary of efficacy and safety was prepared by Glaxo-Wellcome. The content was reviewed for accuracy by the primary FDA medical reviewer, and an attempt was made to resolve any areas of difference, so that these summaries might be viewed as representing the common views of the sponsor and the agency. However, time did not permit peer review of this process, so it is possible that it may be necessary to add to this section the observations of other members of the review team who do not agree with the statements contained in the sponsor's efficacy and safety review. The primary reviewer wishes to note the following:

The reviewer does not dispute the results of analyses such as point-prevalence quit rates, the alternative analysis of Study 405 which excluded patients who dropped out during the bupropion/placebo tablet run-in, or other explorations of the data. However, the outcome prospectively defined as primary is the 4-week, continuous quit rate calculated using the intent-to-treat denominator. Positive results from this analysis are considered by the reviewer to be persuasive. It is recognized that other approaches to analysis may reveal useful findings which generate hypotheses for future testing, and may, in the future, be considered supportive evidence should future studies yield substantially positive results.

The reviewer did not perform an independent search of the MedWatch database to determine the accuracy of all statements made by the sponsor regarding the post-marketing experience with Wellbutrin, nor an independent review of serious adverse events noted in the depression studies. This product was reviewed for safety by the Division of Neuropharmacological Drug Products (HFD-120) using the safety database of the depression studies and post-marketing data, and has been approved for marketing. Significant safety findings noted by the HFD-120 reviewer were addressed in the sponsor's document.

CC: Orig. NDA 20-711
Div. File
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MEDICAL OFFICER REVIEW

NDA: 20-711
SPONSOR: Glaxo Wellcome
DRUG: Bupropion Hydrochloride Sustained Release
TYPE OF SUBMISSION: General Correspondence: Rationale for Different Proprietary Name for Smoking Cessation Indication
PROPOSED INDICATION: Smoking Cessation
MEDICAL OFFICER: Celia Jaffe Winchell, M.D.
PEER MEDICAL OFFICER: Curtis Wright, M.D.
LETTER DATE BY SPONSOR: 7/29/96
DATE RECEIVED BY CDER: 7/30/96
DATE RECEIVED BY REVIEWER: 8/26/96
REVIEW DATE: 9/24/96
CSO: Bonnie McNeal

1.0 Background:
Glaxo Wellcome is developing Bupropion SR for two separate indications: smoking cessation and depression. They would like to market the anti-depressant under the tradename Wellbutrin SR, and the smoking cessation aid under a different tradename. This submission contains a memo delineating their justification for this plan. The main issue of concern is that bupropion has a well-known, dose-dependent risk of precipitating seizures, estimated at 0.1% for doses up to 300 mg/day (as proposed for smoking cessation), at 0.4% for doses 300-450 mg/day (recommended range for antidepressant), with a significant increase in rate for higher doses which could easily be obtained by a patient combining the recommended dose for smoking cessation with the recommended dose for depression. The use of two different names increases the likelihood of inadvertent "double dosing," either by a single practitioner who did not recognize the two medications to be identical, or by two practitioners, with the patient failing to recognize the duplication and draw the physician's attention to it.

2.0 Sponsor's Main Points:
The sponsors cite three main reasons for their proposal for a distinct tradename for the smoking cessation product. First, they mention facilitation of the distribution of educational materials to be used in conjunction with the product for smoking cessation. The sponsor would like to package self-help materials for smoking cessation with the medication, and have a patient package insert geared to this indication. Second, they fear that patients will resist using the medication because it is known as an antidepressant, or that they may face adverse consequences as a result of others learning of and misinterpreting their use of this medication. Through using a distinct tradename, patients would avoid the stigma faced by users of anti-depressants. Third, the sponsor reports that having one tradename for the two very different indications would complicate reimbursement procedures through managed care organizations, and would result in patients failing to receive reimbursement for bupropion even when their policy covers smoking cessation aids.

3.0 Discussion
3.1 Access to behavioral support materials
The first point, **"A distinct tradename for the smoking cessation indication is the most efficient way to ensure that appropriate patients receive appropriate smoking cessation support materials that may increase the likelihood of successful quitting,"** is perhaps somewhat spurious. The product was not tested with a self-help kit, although subjects in some studies were given a self-help manual to read. They also received face-to-face and telephone

counseling; in some studies the behavioral component entailed hour-long group therapy sessions. Certainly, other products have been marketed along with self-help programs that are felt to contribute to efficacy, but there are numerous ways to distribute such a program.

This is a prescription product. Good practitioner education could ensure that prescribers of the medication also facilitate the distribution of the smoking cessation support materials, either by enrolling patients by phone or post-card at the time of prescription, distributing the materials directly from a supply provided by the detail rep, or instructing patients to request the materials from the pharmacist or manufacturer.

On the other hand, the experience with the nicotine replacement products might inspire a certain skepticism about the likelihood of clinicians actually following through with providing behavioral support or even appropriate self-help materials. In one study, nicotine patches provided in a simulated OTC format, packaged with a self-help kit (booklet and tape), had a higher efficacy rate than the same medication provided in the context of physician office visits. Despite the labeling instructing the physician that the medication was to be used as an adjunct to behavioral support, apparently, little is offered. If the manufacturer is planning to provide a significant package of supportive materials with each bottle of medication, then this route may, in fact, be more efficient than relying upon the practitioner to provide materials, even if supplied to the practitioner by the manufacturer. However, if the proposed strategy is to provide a postcard, 800 number, or other mechanism for the patient to access the package, requiring some initiative on the patient's part, it is unclear whether this would be superior to the modes mentioned above.

3.2 Social and economic stigma of mental illness

The second point, **"A separate tradename would minimize any confusion regarding the indication for which the drug is being prescribed. Without this clear distinction, social and economic stigma will discourage access to this promising aid to smoking cessation,"** has, sadly, some merit. Unarguably, patients with affective disorders face stigma, misunderstanding, and discrimination. This discrimination extends not simply to arenas such as social and job opportunities, but is extremely widespread among insurers, who may refuse to issue a policy (or charge exorbitant premiums) to anyone who has made use of psychiatric services. The likelihood that at least some persons prescribed bupropion for smoking cessation will acquire the reputation of "being on an antidepressant" is a concern. Furthermore, patients themselves may resist treatment with a medication they perceive to be an antidepressant because of their own misconceptions and prejudices, and may assume the clinician is implying mental illness on the part of the patient.

This being said, clinicians making use of approved drugs for off-label indications (and some labeled, but less well-known, indications) face this difficulty on a regular basis. Psychiatrists are all adept at explaining, "This drug is actually sold to prevent seizures, but we've found it also works to reduce mood swings, even in people who don't have seizures. No one knows for sure why this is, but we know it works." More to the point, those who manage chronic pain have long known of the utility of the tricyclic antidepressants in treating neuropathic conditions. To be sure, some of their patients resist the notion and may need to be persuaded, but this has certainly not prevented the widespread use of tricyclics for this off-label indication. Other antidepressants are gaining popularity for the treatment of impotence (Trazodone) and premature ejaculation (Prozac). People are willing to take Thorazine for hiccups, imipramine for enuresis, Tegretol for trigeminal neuralgia (even though people with seizure disorders can lose their driver's licenses), Vistaril for itching (labeled for this use but marketed under the same name as the anxiolytic), MAO inhibitors for migraine prophylaxis, and Valium for back spasm. If a patient is troubled by a problem and needs treatment, he will generally be interested in trying what his doctor recommends, whatever else that medication may be used for. If the product works, and gains acceptance among clinicians, it will be used. Doctors should be able to overcome the resistance of most patients using the most persuasive argument of all: this works. Therefore, while the risk of the patient

experiencing misunderstanding and stigma is a concern, the issue of patient lack of acceptance should not be one.

3.3 Managed Care reimbursement

The third point, **"A separate tradename for use in smoking cessation would enable organizations with formularies or restricted reimbursement for antidepressants to reimburse their smoking cessation patients. Marketing the drug for smoking cessation and depression under the same tradename will restrict reimbursement to the drug for use as an aid to smoking cessation and thereby restrict patient access,"** is somewhat surprising. The sponsor reports that the representatives of several managed care organizations revealed that the MCO's are incapable of reimbursing patients for a given medication used for one indication and denying reimbursement for another indication. As some MCO's do not reimburse for antidepressants (or restrict reimbursement for them), the sponsor fears that patients prescribed bupropion for smoking cessation would not receive reimbursement from their insurance carriers, despite having coverage for prescription medications for use in smoking cessation. Quite apart from the appalling notion that MCO's would like to avoid at all costs providing psychiatric care to their members, it is difficult to imagine that the MCO's are incapable of distinguishing between covered and uncovered uses of medication. Virtually every organization has an appeals process, and it would seem that a letter from the doctor returned to the company along with the "explanation of benefits" (EOB) on which the prescription claim was denied would be sufficient to address the MCO's unwillingness to reimburse for bupropion used for smoking cessation. Even the most restrictive organizations (e.g. Maryland Medical Assistance) have a mechanism for providing brand name drug when medically necessary, even if generics are mandated by the policy. It also seems hard to believe (although it may be true) that all the patients using psychotropics for often *off label* use, as discussed above, are doing so out-of-pocket.

3.4 Labeling to manage risk

The fourth point, **"We believe the use of ...labeling will adequately address the potential for double-dosing, while preserving the benefits discussed above for separate tradenames,"** is actually the main one to consider. The real issue is whether the risk of inadvertent simultaneous use of bupropion for two separate indications can be adequately managed through labeling. If not, none of the other arguments are relevant.

4.0 Analysis

4.1 What is the risk?

4.1.1 Seizure incidence rates

The label for the immediate-release formulation of Wellbutrin (bupropion HCl) lists the following seizure rates:

Dose Range	Seizure Incidence
up to 450mg/day	.4%
600 mg/day	2.3%
601-900 mg/day	2.8%

The Division of Neuropharmacologic Drug Products, after reviewing the materials submitted for the Bupropion Sustained Release NDA (for depression), concluded that the immediate-release and sustained-release formulations were bioequivalent, and that the pattern of occurrence of seizures did not support the notion that the SR formulation would contribute to a lowering of seizure risk. A large, open label safety study of the SR formulation used as an antidepressant in **doses of 150-300 mg/day (as proposed for smoking cessation) yielded a seizure incidence of 0.1%,** however, efficacy was not demonstrated at these doses. DNDP concluded the following about the seizure risk of the sustained-release formulation:

Seizures occurring with bupropion don't all occur within the early doses, and as noted earlier, during steady state, there is essentially equivalence regarding both rate and extent of absorption for parent and metabolites for the IR and SR forms when dosing is tid for the IR form and bid for the SR form.

If we were to approve the SR formulation in the currently approved dose range, i.e. 300-400 mg/day, it would be necessary for the labeling to carry the same seizure warning as is currently in place.

Thus, patients taking Wellbutrin or Wellbutrin SR for depression in the recommended doses would be expected to have a seizure incidence of 4/1000; patients taking bupropion SR for smoking cessation, in the recommended dose, would be expected to have a seizure incidence of 1/1000.

As noted above, the danger of inadvertent double-dosing is not insignificant. The minimum effective dose for depression appears to be 300 mg/day; the optimal dose for smoking cessation also appears to be 300 mg/day. Thus, a patient receiving prescriptions for both indications would be very likely to take a combined dose of 600 mg/day *or more*, in which range the incidence of seizures has been demonstrated to be 2.3-2.8%. It would not be necessary that the error go unnoticed for a prolonged period of time: one subject in an open-label study of the safety of bupropion SR for depression experienced a seizure after ingesting 600 mg over a 24-hour period in order to "catch up" on missed doses.

4.1.2 Prescription rates

Wellbutrin (bupropion hydrochloride immediate-release) was originally launched in 1989. Since that time, the sponsor reports that there have been an estimated million Wellbutrin prescriptions, and concludes that this suggests that over 3 million people have been treated with Wellbutrin. Wellbutrin's share of the antidepressant market is small, as many practitioners are put off by the higher seizure risk compared to other available antidepressants.

There are approximately 50 million smokers in the U.S., and there have been more than million new prescriptions for nicotine patches since their initial marketing in 1992, plus million prescriptions for nicotine gum. There is clearly a large market for pharmacological aids to smoking cessation, although it is impossible to predict what share of this market will be captured by bupropion SR.

4.1.3 Comorbidity/Co-prescription

Smoking is common among individuals with affective disorders. It is not unreasonable to envision a significant overlap between smokers and individuals with depression. However, it cannot be predicted how many smokers treated with bupropion SR for smoking cessation might also be in the group of depressed individuals treated with Wellbutrin for depression.

4.2 What is proposed to manage the risk?

The sponsor indicates that both patient and physician labeling for (Tradename TBA) smoking cessation aid would advise against concomitant use of Wellbutrin or Wellbutrin SR along with the smoking cessation product "because each contains the same active ingredient." The labels for Wellbutrin and Wellbutrin SR would contain similar language. The sponsor also endorses a willingness "to explore other mechanisms to minimize the potential for double-dosing," including working with companies that distribute pharmacy terminal software to incorporate a screening question that identifies concurrent use. Furthermore, promotional materials distributed to physicians and patient materials distributed with the product would also contain the information.

4.3 How adequate would this be?

If, indeed, the majority of pharmacies are making use of computerized systems that can be programmed to prompt warnings (drug interactions, etc.) prior to dispensing, this would be a

highly desirable mechanism to employ. However, this would not address the problem of dispensing at smaller pharmacies, doctor's offices (samples), and clinics. Physician and patient education materials would be essential. Warnings in the label itself are, of course, a given. The nature of these warnings, however, is an important issue.

Specifics of proposed labeling are not included in this submission. However, the package insert submitted with the NDA buries the information in the "Precautions" section, where the statement reads "Patients should be made aware that Tradename Sustained-Release Tablets contain the same active ingredient found in Wellbutrin (bupropion hydrochloride) Tablets and Wellbutrin SR (bupropion hydrochloride) Sustained-Release Tablets used to treat depression, and that Tradename Tablets should not be used in combination with either Wellbutrin or Wellbutrin SR Tablets." This seems inadequate.

The statement "contains the same active ingredient" should be strengthened, since the medication is, in fact, identical in formulation (the same drug product), and not a different medication which simply shares the same active ingredient. The placement in the "Precautions" section is insufficiently prominent. One would have to carefully pore through the entire label to find this important warning.

4.4 Is adequate labeling possible?
It is probably possible to prevent most potential inadvertent double dosing through the use of truly un-ignorable warnings in the packaging and promotion of these products. However, the appearance and placement of the warnings would need to be such that any reasonable person would receive an unmistakable message about the dangers of combining the two drugs. To provide several "safety nets," the warning should be included on all materials provided to the physician (Physician Package Insert, promotional materials, advertising, box and bottle label on samples), the pharmacist (Patient Package Insert, box and bottle labels, manufacturer-supplied patient information brochures, computerized drug interactions reminders), and the patient (Patient Package Insert, patient information materials provided by manufacturer, direct-to-consumer advertising, box and bottle label).

Labeling must prominently feature a statement that Tradename is identical to Wellbutrin SR, and that the combination of the two could result in toxicity, including seizures. Patients should be instructed in prominent type, on the box, bottle, and package insert, not to take this medication if they are using any medication for depression, and to alert the prescribing physician

Tradename label: DO NOT USE IN COMBINATION WITH WELLBUTRIN OR WELLBUTRIN SR, or any other product containing bupropion. NOTIFY YOUR DOCTOR If YOU HAVE BEEN PRESCRIBED WELLBUTRIN, WELLBUTRIN SR, OR ANY OTHER MEDICATION FOR DEPRESSION. TRADENAME AND WELLBUTRIN SR ARE IDENTICAL DRUGS, AND TAKING THEM TOGETHER CAN RESULT IN OVERDOSE AND CAN CAUSE SEIZURES.

Wellbutrin label: DO NOT USE IN COMBINATION WITH TRADENAME, or any other product containing bupropion. NOTIFY YOUR DOCTOR If YOU HAVE BEEN PRESCRIBED TRADENAME FOR SMOKING CESSATION. WELLBUTRIN AND TRADENAME ARE IDENTICAL DRUGS, AND TAKING THEM TOGETHER CAN RESULT IN OVERDOSE AND CAN CAUSE SEIZURES.

4.5 Is this overkill?
It can be argued that these labeling requirements are not comparable to those required of other sponsors. In the over-the-counter environment, diphenhydramine is sold under many different

names as an antihistamine, but also under yet other names as a sleep aid. It is possible that a patient could be taking diphenhydramine simultaneously in Sominex and Benadryl, and only the Benadryl label specifically warns against combining with other products containing diphenhydramine. Acetaminophen, not a benign substance in overdose, is present in a myriad of OTC products without warnings about combination with other products containing the same ingredients. In the prescription drug environment, many potentially lethal drug interactions are, in effect, "buried" in the PDR label. Furthermore, many drugs available under different brand names (albeit not for the same drug *product*) could be as dangerous as Wellbutrin (if not more so) if double-dosed; this is also an issue for brand name/generic pairs in which the patient may not realize he has two bottles of the same thing. However, the low therapeutic index (just doubling the dose is hazardous, vs taking a whole bottle of Tylenol) and the severity of the adverse event in question justifies the increased level of concern and the more elaborate efforts to ensure patients are informed about the risk. These labeling features would also need to be incorporated into any future medications containing bupropion.

4.6 Regulatory Issues

It must be accepted that this discussion about the appropriateness of marketing this product under two different trade names exists only because it is identical to another *drug product* already (slated to be) on the market. The identical drug substance could be marketed under a different name, with completely separate directions for use, under a different NDA, as long as it is a different drug *product*: different in any single way – color, manufacturer, packaging (e.g. blister pack), size, shape, etc. Recognizing that, assuming any marketing success for this product, it is only a matter of time before an NDA for a new bupropion-containing drug product is submitted, one must accept that it may be inevitable that two or more such products will exist in the marketplace under various names, and that forcing Glaxo-Wellcome to use one name will only delay, not prevent, the problem.

5.0 Conclusion/Recommendations

The sponsor's proposal should be presented to the Drug Abuse Advisory Committee for input; however, the review division recommends that the request be granted. If the sponsor wishes to market, under two different trade names, similar drug products that have different indications, dosing, and labeling, this would be permissible provided they comply with label warning suggestions similar to those above. For consistency, the portions of the label that are not specific to use in smoking cessation should be identical to the corresponding sections in the antidepressant label, and safety data from both development programs should be included in the smoking cessation label.

11/12/96

Celia Jaffe Winchell, M.D.
Medical Officer
9/24/96

Curtis Wright, M.D.
Peer Reviewer
9/24/95

11/12/96

Archival: NDA 20-711
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MEDICAL OFFICER REVIEW

NDA: 20-711
SPONSOR: Glaxo Wellcome Inc
DRUG: WELLBUTRIN[(Bupropion Hydrochloride) Sustained Release
PROPOSED INDICATION: SMOKING CESSATION
MEDICAL OFFICER: Chang Qing Li, MD, MSHA, DrPH
PEER MEDICAL OFFICER: Celia Winchell, MD
DATE REVIEW COMPLETED: 11/13/96
CSO: B McNeal

Title of Study

A Multicenter Evaluation of WELLBUTRIN[(Bupropion Hydrochloride) Sustained Release, HABITROL (Nicotine Transdermal System), and Combination WELLBUTRIN Sustained Release/HABITROL Treatment Versus Placebo as Aids to Smoking Cessation **(Study 405)**.

Summary

This was a parallel, randomized, double-blind, placebo-controlled trial conducted at four clinical centers. Male and female outpatients aged 18 years and older who were chronic cigarette smokers were eligible to participate. Patients were randomized to one of four treatment groups: PBO, WB SR 300 mg/day, HAB 21 mg/day, or a combination of WB SR 300 mg/day and HAB 21 mg/day. The primary efficacy measure was defined as abstinence from smoking during a specified 4-week period of the Treatment Phase (Weeks 4 through 7).

Four-week continuous quit rates (Day 22 through Day 49) were 49.2%, 36.1%, and 57.6% in the WB SR, HAB, and WB SR/HAB groups, respectively, versus 23.1% in the PBO group in the intent-to-treat population. The differences between the PBO group and each of the active treatment groups were statistically significant in favor of the active treatments ($p<0.01$). The study provided substantial evidence of efficacy of WELLBUTRIN SR 300 mg/day as an aid to smoking cessation.

WELLBUTRIN SR was associated with insomnia, nausea, constipation, disturbed concentration, and dizziness.

Unusual risks of WELLBUTRIN SR appear to be dermatologic hypersensitivity drug reaction (1%), and the combination WELLBUTRIN SR and HABITROL might be associated with hypertension in a small group of people (1%).

INTRODUCTION

Antidepressants have been investigated as aids to smoking cessation, but studies have not generated clear results.

WELLBUTRIN (bupropion hydrochloride) is an aminoketone antidepressant developed by Glaxo Wellcome Inc., and it includes a sustained-release formulation (WELLBUTRIN SR). As an antidepressant, WELLBUTRIN is thought to act primarily via a noradrenergic mechanism, but also has some dopaminergic activity. The most common adverse experiences associated with WELLBUTRIN SR are headache, dry mouth, nausea, dizziness, insomnia, and constipation.

Three studies (Studies 401, 402, and 403) have evaluated WELLBUTRIN and WELLBUTRIN SR as aids to smoking cessation. The WELLBUTRIN SR patients in the 300 mg/day group achieved the best cessation rate among the three different dose ranges.

Objective

The objective of this trial was to evaluate the efficacy and safety of WELLBUTRIN SR (WB SR) 300 mg/day compared to placebo (PBO) as an aid to smoking cessation in chronic cigarette smokers when used in conjunction with brief, individual counseling, and to evaluate the efficacy and safety of combination WB SR/HABITROL (WB SR/HAB) treatment compared to WB SR or HABITROL (HAB) alone as aids to smoking cessation in chronic cigarette smokers when used in conjunction with brief, individual counseling. A secondary objective of this study was to compare the efficacy and safety of WB SR and HAB treatment in chronic cigarette smokers.

Investigators and Locations

Four sites participated in this trial. The investigators were Douglas Jorenby, Ph.D., at the University of Wisconsin Medical School; Scott Leischow, Ph.D., at the University of Arizona; Mitchell Nides, Ph.D., in Los Angeles; and Stephen Rennard, M.D., at the University of Nebraska Medical Center.

STUDY DESIGN

This was a parallel, randomized, multicenter, double-blind, double-dummy placebo-controlled trial involving 893 male and female chronic cigarette smokers. The study consisted of 4 phases: a Screen/Baseline Phase (minimum of 7 days), a 7-week

Treatment Phase, a 2-week Taper Phase, and a 43 week Follow-up Phase. Eligible patients entered the Treatment Phase and were randomized to receive either WB SR 300 mg/day (150 mg b.i.d.), HAB 21 mg/day, combination WB SR 150 mg b.i.d./HAB 21 mg/day, or placebo (PBO). Treatment was provided in conjunction with brief individual smoking cessation and relapse prevention counseling standardized across centers.

3.1 Protocol

3.1.1 Population

Patients were included who:

- were at least 18 years of age
- were in general good health
- were appropriate candidates for prescription of nicotine patches
- weighed at least 100 lbs
- smoked an average of at least 15 cigarettes/day during the past year, with no period of abstinence greater than three months in the past year
- were motivated to quit smoking
- were available for participation in the study for one year.

Patients were excluded who:

- had any predisposition to seizures
- had a history of severe renal, hepatic, neurological, or chronic pulmonary disease.
- had a history of cardiovascular disease, including MI within past 3 months, significant arrhythmias, or poorly controlled hypertension
- had active peptic ulcer disease, serious endocrine disorder, or any other unstable medical disorder.
- had a history or current diagnosis of anorexia nervosa or bulimia
- were experiencing a current major depressive episode, or had a current or past diagnosis of panic disorder, psychosis, or bipolar disorder
- had a history of alcohol or substance abuse within the past year
- had used any psychoactive drug within one week of the Treatment Phase.
- had been treated with nicotine replacement products in past 6 months.
- had used any investigational drug within four weeks of treatment phase
- had a history of skin disorders or allergies, including known sensitivity to any topical nicotine preparations or skin patches, or strong reactions to medical dressings and tapes
- had a current skin disorder, including psoriasis, urticaria, active dermatitis or eczema, even if currently controlled through medication.
- were currently using other smoking cessation treatments including behavior therapy or other medications
- used tobacco products other than cigarettes
- had a history of prior treatment with Wellbutrin or bupropion sustained-release
- were pregnant, nursing, or (female) not using contraception
- had another household member who wished to participate.

3.1.2 Procedures

Interested subjects who responded to advertisements and news releases were evaluated by phone, and if appropriate, were invited to an information session. Attendees who remained motivated to participate were scheduled for a screening visit at which medical history, physical exam, lab tests, electrocardiogram (EKG), chest x-ray (CXR), serum cotinine, smoking history, Structured Clinical Interview for DSM Diagnosis (SCID), Self-Administered Alcoholism Screening Test (SAAST) Questionnaire, adverse experience assessment, concomitant medications review, and exhaled carbon monoxide measurement (CO) were completed.

Patients who satisfied criteria at the initial screening visit were asked to select a target quit date (TQD). The baseline visit was scheduled 8 days prior to the TQD (but no less than seven days after the first visit) to allow for a minimum of 7 days of treatment before the quit attempt. Patients were instructed not to try to quit smoking prior to their TQD. They were given a diary including questions on number of cigarettes smoked, severity of nicotine craving, and withdrawal symptoms.

At the baseline visit, assessments included inclusion/exclusion criteria, vital signs, weight, exhaled CO, adverse experiences, concomitant medications, Fagerstrom Tolerance Questionnaire (FTQ), depression and affect assessments (Beck Depression Inventory (BDI) and Positive and Negative Affect Scale (PANAS)), University of Wisconsin Center for Tobacco Research and Intervention (UWCTRI) Craving and Withdrawal Scale, and a quality of life/resource utilization assessment.

The dosing schedule employed for the four groups is shown in the following table:

Tx Group	Days	Bupropion SR dose			Habitrol Dose (mg)
		AM(mg)	PM (mg)	total	
WB SR	1-3	150	0	150	not applied
	4-7	150	150	300	not applied
	8-63	150	150	300	0
HAB	1-3	0	0	0	not applied
	4-7	0	0	0	not applied
	8-49	0	0	0	21
	50-56	0	0	0	14
	57-63	0	0	0	7
WB SR/HAB	1-3	150	0	150	not applied
	4-7	150	150	300	not applied
	8-49	150	150	300	21
	50-56	150	150	300	14
	57-63	150	150	300	7
Placebo	1-7	0	0	0	not applied
	8-63	0	0	0	0

All subjects who were randomized to treatment also received brief individual counseling to encourage abstinence, provided by a trained clinician at each clinic visit. These were based on information presented in the National Cancer Institute's (NCI) manual, "How to

Help Your Patients Stop Smoking." Telephone contact for counseling was also provided at several time points throughout the follow-up phase.

Clinic visits occurred weekly during the treatment phase, and patients completed daily diaries. At each visit, assessments included vital signs, weight, adverse experiences, concomitant medications, study medication compliance review, UWCTRI Craving and Withdrawal Scale, and exhaled CO. The BDI was repeated at Weeks 3 and 7, the PANAS was repeated at Weeks 2, 3, and 7, and the Quality of Life/Resource Utilization assessment was repeated at Week 7. Blood samples were collected for bupropion levels at Weeks 3 and 6.

Weekly clinic visits occurred during the Taper Phase and patients continued to complete daily diaries. Assessments included those noted above for the Treatment Phase. Counseling sessions continued during this phase.

During the 43-week follow-up phase, which is ongoing, subjects are to be seen at weeks 10 and 12, and at 6 months and 1 year. They are also to be contacted by phone at Week 11, and monthly between Week 12 and one year. At each telephone contact, self-report of smoking will be obtained, and brief counseling will be provided. At clinic visits, assessments will include vital signs, weight, BDI, PANAS, Craving and Withdrawal Scale, exhaled CO, smoking and withdrawal assessments, and quality of life/resource utilization assessment.

Compliance

Study personnel assessed compliance with the dosing regimen and recorded the number of tablets and unused patches returned or documented that the blister card and/or patches were not returned.

Endpoints

Efficacy

The *a priori* primary efficacy measure was abstinence from smoking during a specified 4-week period of the Treatment Phase (Weeks 4 through 7). Abstinence was defined as a patient's report of no smoking (0 cigarettes/day), confirmed by exhaled air carbon monoxide (CO) levels less than or equal to 10 ppm. The intent-to-treat sample included all randomized patients.

Secondary efficacy measures included: continuous quit from Day 22, weekly point prevalence abstinence rates, daily craving and withdrawal symptom scores, weekly UWCTRI craving and withdrawal symptom scores, and number of cigarettes smoked per day by nonquitters per diary data. Depression, quality of life and resource utilization were also assessed.

Safety

Safety assessments included vital signs, weight, and an adverse experience probe.

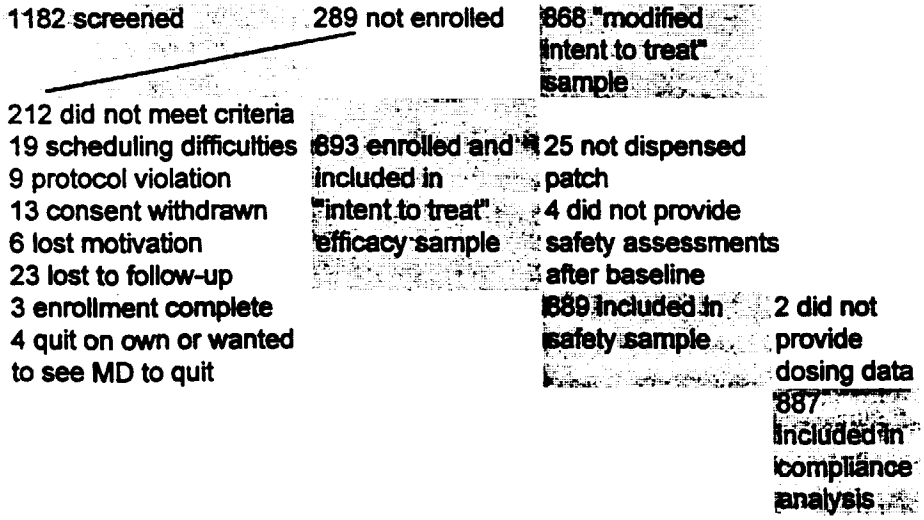
At each clinic visit from Screen through Week 10, adverse experience information was elicited from each patient by study personnel using a verbal probe procedure. The start and cessation dates, any action taken, and an assessment of the intensity, seriousness, and causal relationship of the adverse experience to the study medication were recorded. Adverse experiences which were still present at the end of Week 10 or one week after the patient prematurely discontinued the study drug were recorded as ongoing.

Statistical Considerations

Two-sided tests and confidence intervals with a 0.05 α level of significance were used for treatment comparisons. For analysis of demographic data and baseline characteristics, between-treatment group comparisons were made using ANOVA for continuous variables and chi-square for categorical variables. Between-treatment group statistical comparisons for quit rates were made using the chi-square test. An initial test to determine the effects of treatment, center, and treatment-by-center interaction on quit rate was performed using logistical regression. Chi square tests were performed comparing each of the active treatment groups to each other. Additional analyses were performed to explore the potential effects of gender, age, race, and history of depression.

Patient Disposition

Patient disposition is illustrated in the diagram below.



A total of 1182 subjects entered the screen/baseline phase. Of these, 289 were not randomized to treatment. The investigator classified the reasons for non-entry for each

subject, but the following data were derived from reviewer examination of the line listings with verbatim descriptions of the reasons subjects were not enrolled. There were several who were assigned to different categories by the reviewer and the investigator. The 289 non-randomized subjects include 212 who were not entered into treatment due to inclusion/exclusion criteria. Nineteen had scheduling difficulties that precluded study participation. Nine subjects were discontinued for protocol violations such as failure to keep appointments or follow directions. Six were described as lacking or having lost motivation. Thirteen lost interest or withdrew consent. Four subjects quit smoking prior to randomization or chose to pursue treatment under a physician's care. Twenty-three were lost to follow-up prior to randomization. Three subjects were screened but not randomized because the study enrollment was complete.

Thus, 893 subjects entered the treatment phase and were randomized to treatment groups, with group N's as follows: PBO = 160, WB SR = 244, HAB = 244, WB SR/HAB = 245. Twenty-five patients were discontinued from the study prior to receiving the patch medication. These included 4 randomized to placebo, 7 randomized to WB SR, 3 randomized to HAB, and 11 randomized to WB SR/HAB. The most common reason given was the ill-characterized "consent withdrawn" category. Adverse experiences were cited as reason for discontinuation primarily among subjects receiving active WB SR. Reasons given for discontinuation (as coded by the investigator) are listed below.

	Treatment Group			
Reason for Discontinuation	PBO (N = 160)	WB SR (N =244)	HAB (N = 244)	WB SR/HAB (N = 245)
Adverse Experience	0	4	1	3
Consent Withdrawn	2	2	1	7
Protocol Violation	1	0	1	0
Scheduling Difficulty	1	1	0	1
Total (Percent)	4 (3%)	7 (3%)	3 (1%)	11 (4%)

Results

Demographic Data, Baseline Characteristics, and Smoking History

Demographic and baseline characteristic data are summarized in the following tables. Of the 893 randomized patients, most (93%) were white, and a slight majority (52%) were female. The mean age was 43.3 years (range and 65 patients were 60 years of age or older. Fifty-two percent of the patients were married, 79% had received some formal education beyond high school, and 84% were employed outside their home. Eighteen percent of the patients had a history of major depression (but were not in a major depressive episode at the time of randomization), and 1% had dysthymia. No statistically significant differences were found between treatment groups on any of the demographic or baseline characteristics.

Overall, patients reported smoking an average of 27 cigarettes per day during the past year, and smoking for an average of 26 years. They also reported having seriously tried

to stop smoking an average of three times in the past, but the majority (77%) only managed to stay off cigarettes for periods of six months or less. Patients had an average cotinine level of 363 ng/ml , and an average Fagerström Tolerance Questionnaire score of 7.4. No statistically significant differences were found between treatment groups on any of the smoking history characteristics.

Statistic or Category	Treatment PBO	WB SR	HAB	WB SR/HAB	All Treatments
Patient Age (yrs)					
N	160	244	244	245	893
Mean	42.7	42.3	44.0	43.9	43.3
Std.Dev.	10.17	10.23	10.92	11.63	10.82
Sex					
N	160	244	244	245	893
Female	94 (59%)	126 (52%)	126 (52%)	121 (49%)	467 (52%)
Male	66 (41%)	118 (48%)	118 (48%)	124 (51%)	426 (48%)
Race					
N	160	244	244	245	893
Black	10 (6%)	7 (3%)	11 (5%)	9 (4%)	37 (4%)
Other	1 (1%)	8 (3%)	6 (2%)	10 (4%)	25 (3%)
White	149 (93%)	229 (94%)	227 (93%)	226 (92%)	831 (93%)
Marital Status					
N	160	244	244	245	893
Married	91 (57%)	139 (57%)	110 (45%)	121 (49%)	461 (52%)
Formal Education					
N	160	244	244	245	893
Less than 8th grade	0 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Graduated 8th grade	1 (1%)	1 (0%)	0 (0%)	0 (0%)	2 (0%)
Some high school	8 (5%)	5 (2%)	10 (4%)	4 (2%)	27 (3%)
Graduated high school	30 (19%)	48 (20%)	42 (17%)	41 (17%)	161 (18%)
Some college, technical, voc.	77 (48%)	113 (46%)	123 (50%)	116 (47%)	429 (48%)
Graduated college	29 (18%)	43 (18%)	47 (19%)	43 (18%)	162 (18%)
Beyond college	8 (5%)	15 (7%)	9 (4%)	21 (9%)	53 (6%)
Graduate degree	7 (4%)	20 (8%)	11 (5%)	19 (8%)	57 (6%)

Summary of Smoking History

Statistic or Category	Treatment PBO	WB SR	HAB	WB SR/HAB	All Treatments
Average Number of CPD* During Past Year					
N	158	244	244	245	891
Mean	28.1	25.5	26.5	26.8	26.6
Std.Dev.	10.57	8.76	9.36	9.38	9.46
Number of years smoked					
N	159	244	244	245	892
Mean	26	25	27	27	26
Std.Dev.	9.9	10.5	11.1	11.6	10.9
No. Times Seriously Tried Stop Smoking					
N	159	244	243	245	891
Mean	3	3	3	4	3
Std.Dev.	2.9	4.7	2.4	2.4	3.3
Longest Time Off Cigarettes					
N	159	244	244	245	892
Never	24 (15%)	25 (10%)	29 (12%)	27 (11%)	105 (12%)
>1 Year	19 (12%)	40 (16%)	26 (11%)	39 (16%)	124 (14%)
Other Smokers In Household?					
N	159	244	244	245	892
No	100 (63%)	174 (71%)	175 (72%)	185 (76%)	634 (71%)
Yes	59 (37%)	70 (29%)	69 (28%)	60 (24%)	258 (29%)

Summary of Smoking History

Statistic or Category	Treatment PBO	WB SR	HAB	WB SR/HAB	All Treatments
Ready to Stop Smoking?					
N	159	244	244	245	892
Extremely Sure	108 (68%)	158 (65%)	165 (68%)	165 (67%)	596 (67%)
Quite Sure	51 (32%)	81 (33%)	72 (30%)	77 (31%)	281 (32%)
Fairly Sure	0 (0%)	5 (2%)	7 (3%)	3 (1%)	15 (2%)
Cotinine (ng/ml)					
N	159	240	242	242	883
Mean	158	157	174	163	163
Std.Dev.	177.2	169.9	205.9	166.3	177.3
Median	340	333	346	332	336
Total Fagerstrom Tolerance Score					
N	159	244	244	245	892
Mean	7.5	7.4	7.4	7.4	7.4
Std.Dev.	1.75	1.55	1.72	1.81	1.70
Total SAAST Score					
N	160	244	244	245	893
Mean	4.0	3.5	3.8	3.5	3.7
Std.Dev.	5.01	4.13	4.32	3.39	4.17

Summary of Major Depression History and Dysthymia

Statistic or Category	Treatment PBO	WB SR	HAB	WB SR/HAB	All Treatments
Major Depression History					
N	160	244	244	245	893
No	135 (84%)	193 (79%)	200 (82%)	202 (82%)	730 (82%)
Yes	25 (16%)	51 (21%)	44 (18%)	43 (18%)	163 (18%)
Number of Episodes of Depression					
N	25	51	44	43	163
1	18 (72%)	39 (76%)	35 (80%)	28 (65%)	120 (74%)
2	3 (12%)	8 (16%)	7 (16%)	11 (26%)	29 (18%)
3	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (1%)
4	0 (0%)	0 (0%)	1 (2%)	1 (2%)	2 (1%)
>=5	4 (16%)	4 (8%)	1 (2%)	2 (5%)	11 (7%)
Age at First Depression Episode					
N	25	50	44	43	162
Mean	31.2	27.9	32.0	30.6	30.2
Std. Dev.	10.73	9.89	11.78	10.97	10.67
Median	32.0	28.5	30.0	31.0	30.0
Minimum	13.0	8.0	8.0	12.0	8.0
Maximum	48.0	45.0	57.0	54.0	57.0
Dysthymia					
N	160	244	244	245	893
No	157 (98%)	241 (99%)	242 (99%)	243 (99%)	883 (99%)
Yes	3 (2%)	3 (1%)	2 (1%)	2 (1%)	10 (1%)

As illustrated above, the four treatment groups were comparable at baseline .

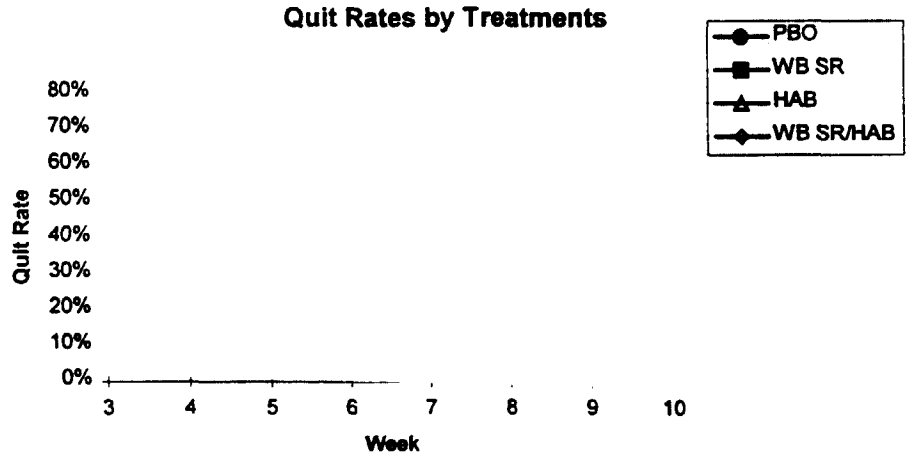
Evaluation of Efficacy

Four-Week Continuous Quit Rates

A total of 386 patients quit smoking for 28 consecutive days during the Treatment Phase (Day 22 through Day 49). The percents of patients who quit smoking during this 4-week period were 49.2%, 36.1%, and 57.6% for WB SR, HAB, and WB SR/HAB, respectively, versus 23.1% for PBO. The 4-week quit rates for the WB SR, HAB, and WB SR/HAB groups were significantly higher compared to the PBO group ($p<0.001$, $p<0.01$, and $p<0.001$, respectively). In addition, the 4-week quit rates for the WB SR ($p<0.01$) and WB SR/HAB ($p<0.001$) groups were significantly higher than the 4-week quit rate for the HAB group. Finally, the 4-week quit rate for the WB SR/HAB group was marginally statistically significantly higher ($p=0.06$) than the 4-week quit rate for the WB SR group. The quit rates by week for the four treatment groups are plotted in the Figure below.

The rates for continuous abstinence were consistently greater for the three active treatment groups compared to the PBO group for the duration of the Treatment and Taper Phases and one week Follow-up.

Similar results on 4-week quit rates and continuous abstinence were observed when patients who had not received both tablet and patch medication were excluded from analysis.



Summary of Continuous Abstinence from Day 22 (Intent-to-Treat)

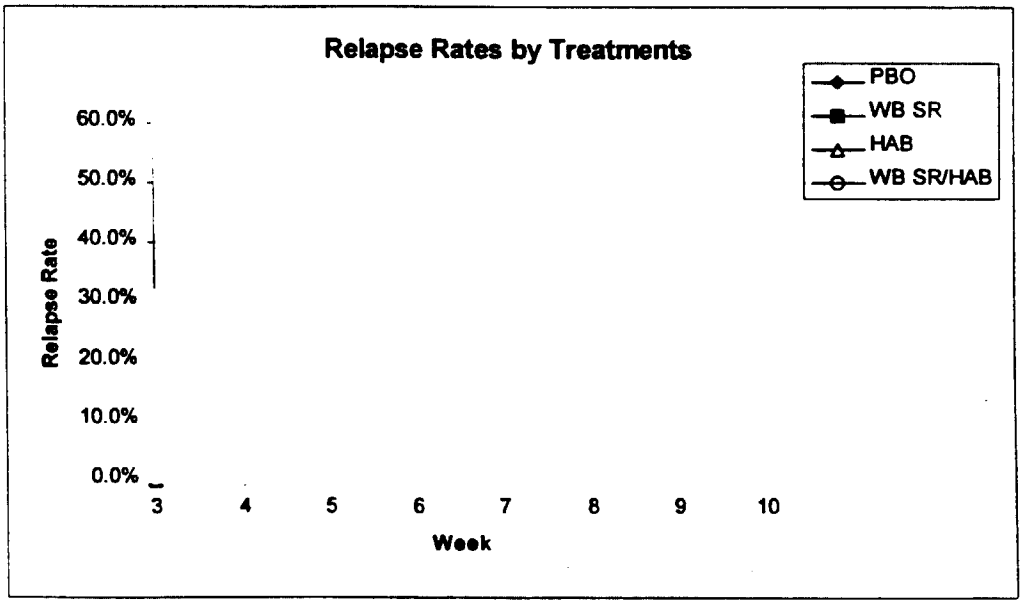
Study Phase	Study Week	Treatment Percentages: PBO N	PBO %	WB SR N	WB SR %	HAB N	HAB %	WB SR/HAB N	WB SR/HAB %	P-Values: PBO vs WB SR	PBO vs HAB	PBO vs WB SR/HAB	WB SR vs HAB	WB SR/HAB vs WB SR	WB SR/HAB vs HAB
Treatment	Day 22*	80	50.0	181	74.2	163	66.8	194	79.2	0.000	0.001	0.000	0.074	0.191	0.002
	4	54	33.8	148	60.7	114	46.7	166	67.8	0.000	0.010	0.000	0.002	0.102	0.000
	5	45	28.1	138	56.6	101	41.4	154	62.9	0.000	0.007	0.000	0.001	0.156	0.000
	6	40	25.0	127	52.0	91	37.3	149	60.8	0.000	0.010	0.000	0.001	0.051	0.000
	7	37	23.1	120	49.2	88	36.1	141	57.6	0.000	0.006	0.000	0.003	0.064	0.000
Taper	8	34	21.3	116	47.5	84	34.4	135	55.1	0.000	0.004	0.000	0.003	0.094	0.000
	9	33	20.6	114	46.7	81	33.2	134	54.7	0.000	0.006	0.000	0.002	0.078	0.000
Follow-Up	10	32	20.0	111	45.5	77	31.6	126	51.4	0.000	0.010	0.000	0.002	0.189	0.000

Verification of Smoking Cessation Data

Review of the data supplied by the sponsor revealed that all subjects, regardless of treatment assignment, recorded as abstinent for longer than 6 week had biochemical verification at week 7. Most CO measurements were conducted as scheduled. Of the patients identified as 4-week quitters, 40 patients (3 PBO, 10 WB SR, 13 HAB, and 14 WB SR/HAB) missed one (n=34) or two (n=6) clinic visits between Weeks 4 and 7 and, therefore, are missing CO values for those visits. All 40 patients had confirmatory CO levels at their next clinic visit and were considered CO confirmed for the 4-week quit analysis. In addition, one quitter (#2143 WB SR) took diazepam up to three times per week for anxiety throughout the study (Screen through Week 10), which was in violation of the protocol.

Smoking Relapse Rate by Treatment Group

The difference in quit rate at Day 22 between the WB SR group and the HAB group was not statistically significant. The HAB and the placebo groups, however, had much higher relapse rate (about 30%) than the WB SR and the WB SR/HAB groups (15-18%) during Week 4 (the first week of continuous abstinence). Then the relapse rate was similar for the active treatment groups. The data suggest that the WB SR and the WB SR/HAB groups achieved better overall quit rate than the HAB group largely due to their effect on relapse control.



Relapse Rates By Treatment Group

Week	PBO	WB SR	HAB	WB SR/HAB
4	32.5%	18.2%	30.1%	14.4%
5	43.8%	23.8%	38.0%	20.6%
6	50.0%	29.8%	44.2%	23.2%
7	53.8%	33.7%	46.0%	27.3%
8	57.5%	35.9%	48.5%	30.4%
9	58.8%	37.0%	50.3%	30.9%
10	60.0%	38.7%	52.8%	35.1%

Efficacy Subgroup Analyses

Results of the 4-week continuous quit rates subgroup analyses by gender, age, race, and history of depression are summarized in the Table below.

No marked differences were seen across groups with the exception of age and history of depression. The 4-week quit rate for the WB SR group was 66.7% in patients ³60 years of age and 48.3% in patients less than 60 years of age; whereas, the quit rates of the other three treatment groups were similar to the quit rates observed in patients less than 60 years old.

The 4-week quit rates were similar across treatment groups in patients with and without a history of depression with the exception of HAB. Four-week quit rates were 27.3% in patients with a history of depression compared to 38.0% in patients without a history of depression. The mean BDI total scores at Baseline were similar for all groups ranging from 3.5 to 4.4 for the three active treatment groups compared to 4.0 for PBO. At the end of the Treatment Phase (Week 7), mean scores for the three active treatment groups ranged from 3.1 to 3.9 compared to 3.8 for PBO.

Results of the 4-week continuous quit rate by-center analysis are not included in the Table. The greatest variations in quit rate were seen in the placebo group. The PBO 4-week quit rates ranged from %. In contrast, the 4-week quit rates for WB SR ranged from %, the 4-week quit rates for HAB ranged from %, and the 4-week quit rates ranged from % for WB SR/HAB. Four-week quit rates for the PBO group were lower than all active treatment groups at all centers. Statistically significant differences in the 4-week quit rates between WB SR/HAB and PBO were noted at all 4 centers.

Summary of 4-Week Continuous Quit Rates Subgroup Analyses

		Treatment Group											
		PBO			WB SR			HAB			WB SR/HAB		
		Subgroup	Quitters		Subgroup	Quitters		Subgroup	Quitters		Subgroup	Quitters	
Subgroup		N	N	%	N	N	%	N	N	%	N	N	%
Gender	Female	94	18	19.1	126	61	48.4[a,b]	126	42	33.3[a]	121	67	55.4[a,b]
	Male	66	19	28.8	118	59	50.0[a]	118	46	39.0	124	74	59.7[a,b]
Age	< 60 yrs	152	35	23.0	232	112	48.3[a,b]	220	80	36.4[a]	224	128	57.1[a,b]
	≥ 60 yrs	8	2	25.0	12	8	66.7	24	8	33.3	21	13	61.9
Race	White	149	33	22.1	229	114	49.8[a,b]	227	82	36.1[a]	226	129	57.1[a,b]
	Black	10	4	40.0	7	4	57.1	11	3	27.3	9	4	44.4
	Other	1	0	0.0	8	2	25.0	6	3	50.0	10	8	80.0[c]
History of Depression	Yes	25	6	24.0	51	26	51.0[a,b]	44	12	27.3	43	24	55.8[a,b]
	No	135	31	23.0	193	94	48.7[a,b]	200	76	38.0[a]	202	117	57.9[a,b]

[a] p< 0.05 versus PBO ; [b] p< 0.05 versus HAB; [c] p< 0.05 versus WB SR

Analyses of Craving

The mean scores at Baseline were similar for all groups: 1.33 for PBO, 1.13 for WB SR, 1.24 for HAB, and 1.03 for WB SR/HAB. The mean score in each treatment group peaked at Week 2, followed by a decrease toward Baseline for the remainder of the Treatment Phase. By the end of the Treatment Phase (Week 7), mean change scores were increased from Baseline by 0.44 for PBO, 0.19 for WB SR, 0.10 for HAB, and 0.02 for WB SR/HAB. Statistical analysis of the craving change scores is presented in the Table below. Statistical significance in favor of HAB versus PBO was demonstrated at most points (Weeks 2-6, 8, and 9, p£0.05). Statistical significance in favor of WB SR versus PBO was demonstrated only at Week 2. Statistical significance in favor of WB SR/HAB over PBO was also noted at Week 2 and at Weeks 5 through 9. The data clearly show that the HAB treatment had a stronger effect on "craving" than the WB SR treatment when compared to the placebo. Thus, the high quit rate achieved by the WB SR group can not be explained by the reduction in "craving".

Patient Daily Diary Data: Craving Summary of Change Scores by Treatments

Study Phase	Study Week	Treatment Means								P-Values					
		PBO		WB SR		HAB		WB SR/HAB		PBO vs			WB SR	WB SR/HAB	
		N	Mean	N	Mean	N	Mean	N	Mean	WB SR	HAB	WB SR/HAB	vs HAB	vs WB SR	vs HAB
Treatment	1	152	-0.14	236	-0.07	237	-0.20	235	-0.10	0.277	0.356	0.563	0.023	0.566	0.090
	2	146	1.13	221	1.05	228	0.94	226	0.97	0.036	0.005	0.010	0.429	0.596	0.794
	3	127	0.84	214	0.61	218	0.50	220	0.57	0.147	0.032	0.081	0.426	0.738	0.641
	4	117	0.66	205	0.47	210	0.33	210	0.35	0.249	0.050	0.061	0.342	0.397	0.317
	5	110	0.65	200	0.34	198	0.26	209	0.18	0.064	0.013	0.006	0.733	0.293	0.482
	6	102	0.52	193	0.22	189	0.18	204	0.12	0.074	0.040	0.017	0.743	0.480	0.711
	7	96	0.44	189	0.19	179	0.10	199	0.02	0.161	0.056	0.020	0.528	0.263	0.642
Taper	8	93	0.44	188	0.12	172	0.07	196	0.01	0.061	0.038	0.015	0.774	0.488	0.698
	9	89	0.41	183	0.06	169	0.05	196	-0.00	0.060	0.051	0.026	0.903	0.690	0.790
Follow-Up	10	86	0.29	179	0.11	161	0.15	190	0.09	0.327	0.455	0.294	0.790	0.940	0.732

*Craving for a Cigarette Now: 5-Point Scale (0-4)

Analyses of Withdrawal Symptom Scores

The mean change scores for the eight individual withdrawal symptoms are analyzed. A summary of the timepoints that reached statistical significance between treatment comparisons is presented in the table and charts below.

For seven of the symptoms, statistically significant differences favoring one or more of the active treatment groups compared to PBO were identified. All three active treatment groups compared favorably to PBO on the symptoms "irritability, frustration, or anger," "anxiety," and "difficulty concentrating" with WB SR and WB SR/HAB having more timepoints of significance than HAB. WB SR and WB SR/HAB also compared favorably to PBO at multiple timepoints on the symptoms of "depressed mood," and "restlessness." Finally, WB SR/HAB had more timepoints that reached statistical significance on the symptom "increased appetite" than did WB SR or HAB alone. Significant differences in mean change scores that favored WB SR/HAB over HAB were also observed for "depressed mood" at Weeks 3, 6, 9, and 10 (p£0.05), for "irritability, frustration, or anger" at Weeks 4, 6, and 9 ($p<0.05$), and for "increased appetite" at Weeks 1-3, 6, and 7 (p£0.05).

The capacity of WB SR to enhance the reduction of the symptoms of withdrawal compared to HAB, especially in preventing early smoking relapse, may explain its efficacy in smoking cessation. The combination treatment of WB SR and HAB may provide the additional help in initiation and early maintenance of smoking abstinence.

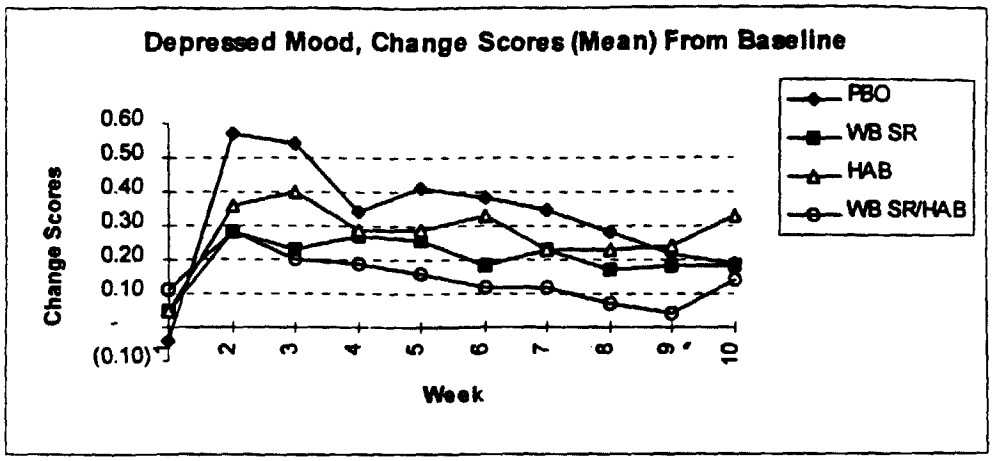
Summary of Nicotine Withdrawal Data Comparisons

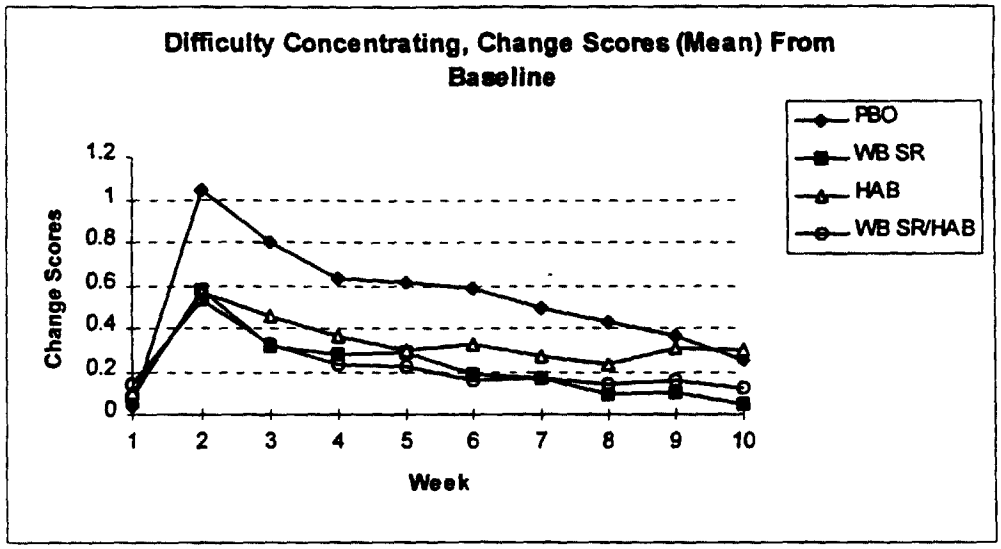
	WB SR and PBO Comparisons										HAB and PBO Comparisons										WB SR/HAB and PBO Comparisons									
Week	1[a]	2	3	4	5	6	7	8	9	10	1[a]	2	3	4	5	6	7	8	9	10	1[a]	2	3	4	5	6	7	8	9	10
Composite score	o	x	x		x	x	x	x				x	x	x	x		x	x			o	x	x	x	x	x	x	x		
Depressed mood	o	x	x			x						x									o	x	x		x	x	x	x		
Difficulty falling asleep	o																				o	o								
Awakening at night	o																	x			o	o	o							
Irritability, frustration or anger	o	x	x	x	x	x		x				x	x	x	x	x					o	x	x	x	x	x	x	x		
Anxiety		x	x	x	x	x	x	x	x			x	x	x	x	x	x	x				x	x	x	x	x	x	x	x	
Difficulty concentrating		x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x				x	x	x	x	x	x	x	x	
Restlessness	o	x	x	x	x	x	x	x			o	x	x		x						o	x	x	x	x	x	x	x		
Increased appetite		x	x			x						x	x	x								x	x	x	x	x				

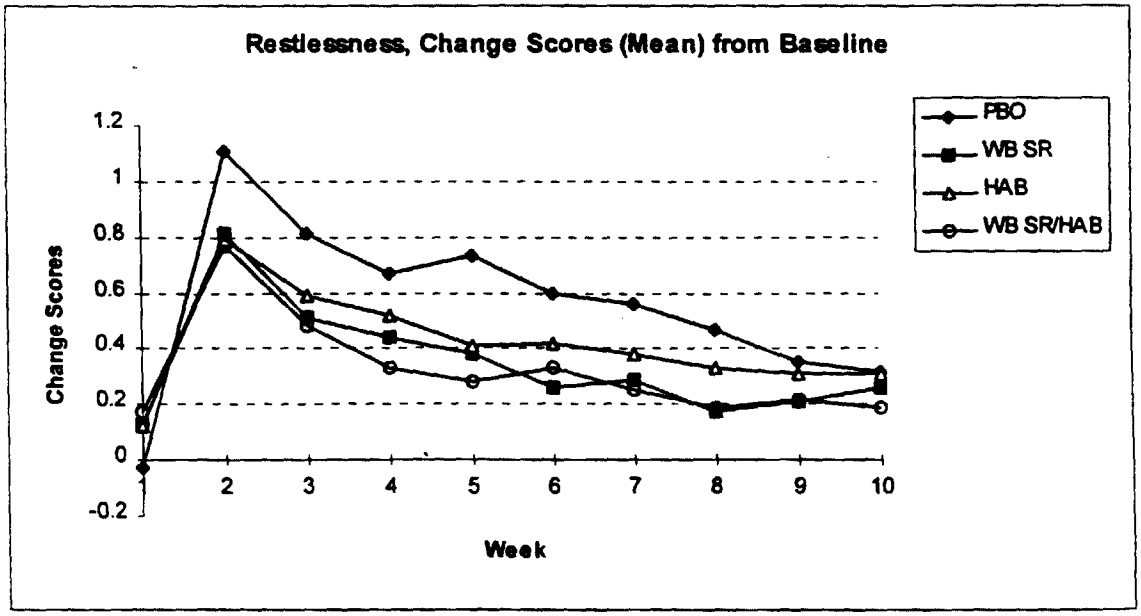
[a] Patch therapy was not initiated until Week 2

x Favors the active treatment over PBO p≤ 0.05

o Favors PBO over the active treatment p≤ 0.05


Depressed Mood, Change Scores (Mean) From Baseline
PBO
WB SR
HAB
WB SR/HAB
Change Scores
0.60
0.50
0.40
0.30
0.20
0.10
-
(0.10)
1
2
3
4
5
6
7
8
9
10
Week


Difficulty Concentrating, Change Scores (Mean) From Baseline
PBO
WB SR
HAB
WB SR/HAB
Change Scores
1.2
1
0.8
0.6
0.4
0.2
0
1
2
3
4
5
6
7
8
9
10
Week


Restlessness, Change Scores (Mean) from Baseline
PBO
WB SR
HAB
WB SR/HAB
Change Scores
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
2
3
4
5
6
7
8
9
10
Week