CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-711/SE8-012

Medical Review(s)

NDA: 20-711/SE1 Serial No. 012
Sponsor: GlaxoWellcome
Principal Investigator:
Drug Name: ZYBAN (bupropion hydrochloride)
Type of Submission: Efficacy Supplement
Proposed Indication: An Aid to Smoking Cessation Treatment: Efficacy in Patients With COPD
Reviewer: Harold Blatt, D.D.S.
Team Leader: Celia Winchell, M.D.
Letter Date by Sponsor: April 26, 2000
Date Received by CDER: April 27, 2000
Date Received by Reviewer: August 28, 2000
Date Review Completed: November 1, 2000
CSO: Judith Milstein

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EXECUTIVE SUMMARY

RECOMMENDATIONS

The efficacy and safety of Zyban, 300 mg/day given to patients with mild to moderate COPD, has been demonstrated in this clinical trial. The efficacy ratio, as compared to placebo, mimics the results in 2 earlier trials performed as part of the original NDA in a larger general population but at a slightly lower rate. Previous trials in the general population showed continuous quit rates of 36% and 49% vs. 28% in this group of COPD patients. A possible explanation for this may be that as a population, COPD patients are more resistant to smoking cessation therapies. Such patients are somewhat older, less healthy, and have a history of more intense long-term chronic smoking habits. They feel the need to smoke despite their having mild to moderate COPD and have difficulty accepting smoking cessation therapies.

The adverse events profile for this group of COPD patients appears to be very similar to that found in the general population.

It is the opinion of this reviewer that this supplement NDA 20-711/SE1 #012 can be approved from a clinical standpoint provided the marked up proposed draft labeling is agreed to by the sponsor and instituted.

SUMMARY OF CLINICAL FINDINGS

A. Brief overview of clinical program.

The sponsor has submitted this Efficacy Supplement for Zyban Sustained Release Tablets. They submitted one trial with an ITT population of 200 placebo patients and 204 Zyban patients to study the efficacy and safety of their drug on patients with mild to moderate COPD. The trial was a multi-center, comparative, randomized, double-blind, placebo-controlled, parallel group study.

B. Efficacy.

The primary efficacy endpoint was the continuous abstinence rate for the period of weeks 4-7 of the Treatment Period. The study drug achieved a statistically significant difference in continuous quit rates over placebo of 28% vs. 16% with a p value of 0.003. The study drug also achieved a statistically significant difference in continuous quit rates over placebo for weeks 9-12 of 22% to 12% with a p value of 0.015. Continuous quit rates were defined as patient self report of not smoking (0 cigarettes/day) and confirmed by expiratory volume of carbon monoxide levels of $\leq$ 10 ppm. The use of Zyban in conjunction with nicotine replacement therapy was not studied in this population.

C. Safety

Two hundred and four patients were exposed to study drug for 12 weeks in this study. The 40-week extension study results will be submitted in November, 2000. There were no deaths reported in the study related to Zyban. There was one serious side effect in the Zyban group of lower extremity occlusion that was corrected by a left femoral tibial bypass. This SAE does not appear to be related to the medication. The most common side effects in the Zyban group were insomnia 24%, nausea 8%, and dry mouth 6%, and headache 6%. [Vol. 57.2, p.65.] Because of the inhibitory effects of Zyban (bupropion) on CYP2D6, patients on psychoactive drugs were specifically excluded from participation in the study. The sponsor has included in their new proposed draft labeling a section on the danger of using Zyban in conjunction with drugs that are metabolized by CYP2D6 such as tricyclic and SSRI antidepressants, beta-blockers, anti-arrhythmics, and anti-psychotics. The ratio of exposure to drug in the trial compared to the probable marketing exposure appears to be adequate. This study exposed patients to drug for 12 weeks with a 40-week extension study. That label recommends use for from 7-12 weeks with up to a 6-month extension for maintenance. Other than nicotine replacement therapies, this reviewer is unaware of any other drugs that are used for smoking cessation that provide a mechanism of action similar to Zyban. The nicotine replacement therapies are often associated with dyspepsia, nausea, diarrhea, hiccup, and hypertension. Nicotine overdose can result in vomiting, headache, dizziness, hypotension, tremor, mental confusion, and, in extreme cases, lead to respiratory failure or cardiac failure. The label does note that Zyban can be used with a nicotine trans-dermal system but that there should be monitoring for treatment emergent hypertension in patients using these drugs in combination.

C. Dosing.

The dosing level for patients with mild to moderate COPD is the same as has been recommended for the general population. That is, no more than 300mg/day given two times daily. While there is a risk from seizure at daily dosing levels in excess of 300mg/day, there were no reported cases of seizures during this trial. As Dr. Winchell mentioned in her review of November 15, 1996, "a seizure incidence of 1/1000 can be expected in the dose range used for smoking cessation, assuming precautions are taken to exclude patients with predisposition to seizure." The existing Warning section of the label discusses in boldface the concern about the dose dependent risk of seizures. This reviewer feels that there is a need to continue to closely monitor for post-marketing reports of seizures with this drug.

D. Special populations.

Females had slightly lower quit rates than males (16% vs. 25%). Subjects over 60 had a higher quit rate than those under 60 (35% vs. 25%). Racial subgroup analysis was too small to provide a clear pattern. It should be noted that subsequent to this submission, the sponsor has been issued a Pediatric Written Request to study Zyban in adolescent smokers.

SECTION I INTRODUCTION AND BACKGROUND

Buproprion hydrochloride was originally developed as an anti-depressant and approved in 1989 in an immediate release form and in a sustained release form in 1997. The most common adverse events (AEs) included constipation, dizziness, dry mouth, headache, insomnia, and nausea. It was approved as ZYBAN in 1997, as a sustained release tablet for smoking cessation.

In the sponsor's introduction, it states that many smoking attributable deaths are due to complications from COPD, which is defined by the American Thoracic Society as airflow obstruction due to chronic bronchitis or emphysema. The definition further divides the disease into three stages. Stage I COPD or mild disease is defined as patients having a Forced Expiratory Volume in 1 second (FEV_1) of at least 50% of predicted. Stage II or moderate disease is defined as a FEV_1 of 35-49% of predicted. Stage III or severe disease is defined as an FEV_1 of < 35%. All COPD patients are also defined as having impaired airways, and signs and symptoms of chronic bronchitis or emphysema. Many patients may have smoking related small airways disease or asymptomatic COPD (no symptoms of mucous hypersecretion).

This supplement consists of only one study (Study AK1A4013) that studied patients with mild or moderate COPD as evidenced by pulmonary function criteria, emphysema, chronic bronchitis, or small airways disease. Patients with severe COPD were excluded from this study because of concern that they would have concurrent illnesses that would require intervention during the study period. [Vol. 57.2, pp. 25-26.] This new study attempts to show both the efficacy and safety of Zyban as compared to placebo as evidenced by quit rates and the adverse events profile respectively.

SECTION A PROPOSED INDICATION

For use as an aid to smoking cessation.

SECTION II CLINICALLY RELEVANT FINDINGS

According to Dr. Celia Winchell's Medical Officer Review of November 15, 1996, the original indication was all adult smokers and there was no statement about a minimum level of smoking. This efficacy supplement and the current proposed draft label it contains, proposes to include in the indication patients with chronic obstructive pulmonary disease (COPD). Such patients were specifically excluded from the Comparative Study 405 and the Dose Response Study 403 in the original NDA for Zyban.

SECTION III REVIEW METHODS

SECTION A FINANCIAL DISCLOSURE

On April 26, 2000 the sponsor submitted Certification: Financial Interests and Arrangements of Clinical Investigators form FDA 3454 and Disclosure: Financial Interests and Arrangements of Clinical Investigators form FDA 3455. These forms certify that the sponsor has not entered into a financial arrangement with the investigator that is dependent on the outcome of the study. Further, that the investigator has not disclosed any proprietary interest in the product or equity in the sponsor's company. These statements appear to satisfy the financial disclosure requirements.

SECTION B DATA QUALITY AND INTEGRITY

No investigation of the trial sites was performed by DSI. This reviewer examined the data line listings regarding continuous quit rates for weeks 4-7 of the Treatment Phase (the primary efficacy variable) and compared them with the sponsor's tables and Summary results. No discrepancies in quit rates were found (based on exhaled CO measurements). [Vol. 57.11, Listing 30, pp. 208-328, Vol. 57.2, pp. 54-55.]

There were 2 reports of patient deaths neither of which occurred during the treatment Phase [Vol. 57.2, p.65], one serious adverse event and 20 reports of discontinuations due to adverse events. The sponsor provided Case Report Forms with the original submission of this supplement. Therefore, this reviewer examined the Case Report Forms as well as the line listings to compare to the sponsor's tabular data to verify data integrity. No discrepancies were found.

Both deaths occurred in patients randomized to the placebo group. One patient died in a car accident and the second death resulted from cardiac arrest secondary to an upper GI bleed.[Vol. 57.3, pp. 2-10 Listing 1, Randomization Schedule, Vol. 57.11, p.331, and Vol. 57.12, p. 198.]

Of the 20 discontinuations due to AEs, 11 occurred in the ZYBAN group as follows: Subject 5309 withdrew due to AEs of anxiety, nausea, generalized, asthenia, anorexia, agitation, vertigo, and insomnia, Subject 5314 due to headache and anxiety, Subject 5384 due to unresolved hypertension, Subject 5397 due to anxiety, Subject 5407 due to agitation (jitters), headache, and nausea, Subject 5458 due to increased anxiety and insomnia, Subject 5600 due to urticaria, Subject 5717 due to confusion, and tremor, Subject 5813 due to tremor, Subject 5834 due to insomnia, and Subject 5847 due to anxiety and insomnia. [Vol. 57.3, Listing 15, pp. 361-366.] See table on next page:

SUBJECT NUMBER	REASONS FOR DISCONTINUATION
#5309	Anxiety, nausea, generalized asthenia, anorexia, agitation, vertigo, and insomnia
#5314	Headache and anxiety
#5384	Unresolved hypertension
#5397	Anxiety
#5407	Agitation (jitters), headache, and nausea
#5458	Increased anxiety and insomnia
#5600	Urticaria
#5717	Confusion and tremor
#5813	Tremor
#5834	Insomnia
#5847	Anxiety and insomnia

There was one serious AE in the ZYBAN group. A 62-year-old patient developed lower extremity occlusion 47 days after beginning therapy. Study drug was interrupted and a left femoral tibial bypass was performed. Complete resolution was seen 45 days after onset. Occlusion was judged not related to the study medication. [Vol. 57.2, p.74.]

SECTION IV DESCRIPTION OF DATA SOURCES

Number of Subjects in Analysis Populations

	Placebo	ZYBAN
Enrolled Population	N=205	N=206
Intent-To-Treat Population	N=200	N=204
Protocol Compliant Population	N=159	N=166

[Taken from sponsor's table Vol. 57.2, p.48.]

Note: Five patients randomized to placebo and 2 patients randomized to ZYBAN were lost to follow-up after their baseline visit. There was no verification of exposure to drug and they were not included in ITT population.

It should be noted that in the table below the Zyban and placebo groups were similar in regard to the types and severity of their COPD and their underlying illnesses.

Summary of Baseline Pulmonary Function Tests and Respiratory Diseases

	Placebo (N=205)	ZYBAN (N=206)
Stage I COPD	85%(175)	85%(175)
Stage II COPD	15%(30)	15%(31)
% of Patients with sub-diagnosis:		
Emphysema	41%(84)	38%(78)
Chronic bronchitis	67%(137)	66%(136)
Emphysema and chronic bronchitis	24%(50)	19%(40)
Small airways disease	17%(34)	16%(32)

[Based on sponsor's Table 7, Vol. 57.2, p.86.]

Baseline demographic information based on the ITT population between the Zyban and placebo groups also appear to be similar with regard to sex, age race smoking history and COPD stage. For Baseline Demographic Information in the ITT Population see table below:

SUBGROUP	PLACEBO n=200	ZYBAN n=204
SEX:		
Male	110 (55%)	112 (55%)
Female	90 (45%)	92 (45%)
AGE:		
<60	138 (69%)	153 (75%)
≥60	62 (31%)	51 (25%)
RACE:		
White	192 (96%)	191 (94%)
Black	7 (4%)	7 (3%)
Other	1 (0.5%)	6 (3%)
SMOKING HISTORY (PACK YEARS):		
≤20	5 (3%)	3 (2%)
>20 to ≤30	38 (19%)	32 (16%)
>30 to ≤40	40 (20%)	35 (17%)
>40	117 (59%)	134 (66%)
COPD STAGE:		
Stage I	170 (85%)	173 (85%)
Stage II	30 (15%)	31 (15%)

[Based on sponsor's Table Vol.57.2, p.61]

LITERATURE SEARCH

No specific safety concerns were noted. For a complete listing see Attachment I.

SECTION V REVIEW OF EFFICACY

Protocol Number AK1A4013

Protocol Synopsis:

Title: A Multi-center Evaluation of the Effects of ZYBAN (buproprion hydrochloride sustained release tablets) versus placebo in a Population of Smokers with COPD: Treatment Phase

Objectives: To demonstrate the safety and efficacy of ZYBAN versus placebo as an aid to smoking cessation in a patient population with mild to moderate COPD.

Study Design: This was a multi-center, comparative, randomized, double-blind, parallel group study in patients with mild to moderate COPD. Four hundred and four subjects (204 in the ZYBAN group and 200 in the placebo group) were randomized to receive either ZYBAN 150 mg or placebo 150 mg in a 1:1 ratio once a day for the first 3 days then twice a day thereafter for the remaining 12 weeks of the study. At the time this review is being written, a 40-week Follow-up phase is still ongoing. However, the sponsor informed us that they will submit a safety update for the Follow-up phase in November, 2000. Please See SAFETY UPDATE SECTION.

The primary efficacy endpoint was defined by the sponsor as subjects who were continuously abstinent (not even 1 puff) confirmed by expiratory CO≤10 ppm during the period of weeks 4-7. Smoking cessation and cigarettes/day end-points were measured by patient self report using daily diaries and confirmation with CO measures (< 10 ppm) at each clinic visit. Because the quit rate should be based on the end of treatment at 12 weeks, the Division feels that the proper primary endpoint should be the continuous abstinence quit rate for the last month of the study (that is weeks 9-12) as confirmed by expiratory CO≤10 ppm.

Secondary efficacy measures included: The DSM-IV Severity of Nicotine Withdrawal Symptoms questionnaire and the University of Wisconsin Center for Tobacco Research and Intervention (UWCTRI) questionnaire measured craving and withdrawal symptoms. Depression symptoms were measured on the Beck Depression Inventory. Analyzing adverse events, vital signs, and weight assessed safety. [Vol. 57.2, pp. 8-9.]

SECTION A PROTOCOL AMENDMENTS

Amendment I was submitted July 13, 1998 and included additional background information and expanded the definition of COPD to include small airway disease, made the protocol consistent with current source documentation and electronic CRFs, complied with FDA guidelines to remove cancer and overdose from the definition of SAE, clarified collection of AEs, and updated the reference list.

Amendment 2 was submitted June 15, 1999. It included a genetics protocol and consent form, and incorporated a genetics sub-study that was voluntary for study sites and subjects.

Amendment 3 was submitted June 15, 1999 and deleted Appendix 1 Zyban package insert to comply with sponsor's SOPs and updated Appendix 5 with new information on procedures to be followed for overdose of ZYBAN. [Vol. 57.2, pp.28-29.]

Statistical Analysis:

All efficacy analyses were performed for the ITT population and for the protocol-compliant population. The primary efficacy endpoint was defined to be the continuous abstinence rate from the period of Week 4 through Week 7 (inclusive) during the 12-week Treatment phase of the study for subjects in the ITT population. Smoking abstinence was defined as subject self report of not smoking (0 cigarettes/day) and confirmed by expiratory carbon monoxide (CO) levels $\leq$ 10 ppm. Comparison of the treatment groups was carried out via a chi-square test on the proportion of subjects in each treatment group that are not smoking at the end of week 7.

Secondary efficacy endpoints measuring abstinence rates were also examined via chi-square tests. These endpoints included point prevalence rates at each visit during the Treatment phase and continuous abstinence rates from day 22 (week 4) through day 84 (week 12) during the Treatment phase. [Vol. 57.2, p. 9.]

See Biostat review for a more complete discussion to statistical issues..

Study Conduct:

Protocol deviations included 53 (31placebo/22 Zyban) patients on study medication for less than 28 days, 4 (2 placebo/2 Zyban) patients who had concurrently taken psychoactive medication for more than 7 days, 2 placebo patients concurrently taking other smoking cessation medications (nicotine patch), and 4 (1 placebo/3 Zyban) patients who had over the pulmonary function ratios mentioned in the inclusion criteria. These last 4 patients had COPD symptoms in the form of chronic bronchitis and were allowed in to the study. This reviewer checked the number given in the sponsor's narrative against the Listing of Major Protocol Violations and found that they match exactly. [Vol. 57.2, p. 50, and Vol. 57.3, Listing 12, pp. 260-261.]

PROTOCOL VIOLATION	ZYBAN GROUP n=204	PLACEBO GROUP n=200
On study medication for less than 28 days	22 (11%)	31 (16%)
On concurrent psychoactive medication for more than 7 days	2 (1%)	2 (1%)
On other smoking cessation medications concurrently	0 (0%)	2 (1%)
Pulmonary function ratios > 70%	3 (2%)	1 (.05%)

Sponsor's Efficacy Results:

Approximately twice as many subjects in the ZYBAN group remained abstinent throughout the 4-12 week Treatment phase as in the placebo group. In the ITT population 89 patients (57 Zyban/32 placebo) were totally abstinent for weeks 4-7. This difference was statistically significant for both critical study end points: 4-7 week (28% vs. 16%, p=0.003) and 9-12 week (22% vs. 12%, p=0.015) continuous abstinence. Please note that the Division prefers the primary endpoint as continuous abstinence for the last four weeks of the study (weeks 9-12). The Division and this reviewer feel that a continuous quit rate at the end of the study is more indicative of the true quit rate than at the 4-7 week period. Therefore, we feel that the primary efficacy variable should be the continuous quit rate for weeks 9-12. It should be noted that the p value at 9-12 weeks still indicates significance at this time period. [Vol. 57.2, pp. 54, 110-111.]

The ZYBAN group had lower scores for Depressed Mood, Irritability- Frustration- or Anger, Anxiety, and Difficulty Concentrating based on the DSM-IV Severity of Nicotine Withdrawal Symptoms questionnaire. However, scores for restlessness, difficulty falling asleep, and increased appetite was about the same for Zyban and placebo groups. Also, placebo patients showed lower scores with regard to awakening at night. The ZYBAN group also showed lower scores of Anger, Anxiety, Difficulty Concentrating, Sadness, Urge to Smoke and Negative Affect on the UWCTRI and WSWS craving and withdrawal scales. Urge to Smoke and Craving scores were also lower for ZYBAN during the last 6 weeks of treatment at weeks 7, 10 and 12. Again, however, scores for sleep problems were much lower in the placebo group.

The sponsor's subgroup analyses of week 4 to 7 continuous abstinence rates show that female subjects had slightly lower abstinence rates than male subjects (16% vs. 25%). Subjects over 60 years of age had a higher quit rate in both ZYBAN and placebo groups than did those under 60 (for the Zyban groups 35% for those over 60 vs. 25% for those under 60). Racial subgroup analysis numbers were too small to provide a clear pattern. Those subjects with less severe COPD (Stage I) generally showed higher quit rates overall. However the difference in efficacy (ZYBAN vs. placebo) was greatest in those with Stage II COPD (OR=3.1). Similarly, those with >30 pack-years of cigarette addiction responded relatively better to ZYBAN vs. placebo than did those with <30 pack-years of smoking (OR=2.32 vs. 1.51). [Vol. 57.2, pp. 10, 54, 59-60.] For a more

complete discussion and analysis of these results, see Biostat review. See sponsor's tabular representation below of continuous quit rates by subgroups:

Weeks 4 to 7 Continuous Abstinence rate by Subgroups: ITT Population

Subgroup	ITT population Placebo n/N (%)*		ZYBAN n/N (%)*		Odds Ratio
Sex					
Male	22/110	(20%)	34/112	(30%)	1.7
Female	10/90	(11%)	23/92	(25%)	2.7
Age					
< 60	19/138	(14%)	39/153	(25%)	2.0
≥ 60	13/62	(21%)	18/51	(35%)	2.0
Race					
White	32/192	(17%)	52/191	(27%)	1.8
Black	0/7	(0%)	4/7	(57%)	
Other	0/1	(0%)	1/6	(17%)	
Smoking history (pack-years)					
≤ 20	2/5	(40%)	1/3	(33%)	0.7
>20 to ≤ 30	7/38	(18%)	9/32	(28%)	1.8
>30 to ≤ 40	7/40	(18%)	11/35	(31%)	2.0
> 40	16/117	(14%)	36/134	(27%)	2.3
Baseline Fagerström score					
≤ 6	15/75	(20%)	24/66	(36%)	2.3
>6	17/124	(14%)	33/138	(24%)	1.9
History of major depression					
No	27/154	(18%)	54/167	(32%)	2.1
Yes	5/46	(11%)	3/37	(8%)	0.7
COPD Stage					
Stage I	30/170	(18%)	51/173	(29)	1.9
Stage II	2/30	(7%)	6/31	(19%)	3.1

*N = total number in subgroup population, n= Number of Quitters
Source = tables 112 to 118
[Vol. 57.2, p.61.]

The subpopulation of COPD patients tends to be more resistant to smoking cessation treatment because they have a longer history of smoking (nicotine addiction) and continue to smoke even though they have active disease. While their continuous quit rates are lower than for the general population, the continuous quit rate ratio of test drug to placebo stays approximately the same. The table below compares the continuous quit rates from 3 trials. The dose response and comparative trials were part or the original NDA and utilized a general population that did not include patients with COPD:

4-7 Week Continuous Quit Rates

	ZYBAN 300mg/day	Placebo
Dose response trial	56/156, 36% (n=156)	26/151, 17% (n=151)
Comparative trial	120/244, 49% (n=244)	37/160 23%, (n=160)
COPD trial	57/204, 28% (n=204)	32/200, 16% (n=200)

[Based on Vol. 57.1, pp. 24-26 and Vol. 57.2, p.55.]

The sponsor has included as a secondary efficacy variable that is referred to as "slips allowed" or "slips analysis". It is defined as an abstinence or quit rate that includes patients who have smoked for a maximum of 6 consecutive days or 9 total days at any time during the Treatment Phase. The results of this analysis showed for weeks 9-12, a 20% quit rate in the placebo group and a 37% quit rate in the Zyban group with a p value of < 0.001. [Vol. 57.2, p.56.] This reviewer feels that this variable does not add anything of a practical value to the evaluation of this drug. It should also be noted that in the original NDA a continuous quit rate was the standard by which the drug's efficacy was judged. Therefore, the review of this drug is based on the primary efficacy variable of continuous quit rates for the 9-12 week period of the Treatment phase.

SECTION VI REVIEW OF SAFETY

Safety was assessed via adverse event reports, vital signs assessments and weight assessments throughout the Treatment phase. Adverse events (AEs) were grouped by treatment group according to body system. Changes in vital signs and weight were computed for each subject and summary statistics were produced for this variable. [Vol. 57.2, p.9.]

This reviewer also looked at a representative sampling of 9 AEs from this study (AK1A4013) and compared them to the results of the studies in the current approved label. These results are generally in line with the reports listed in the label from previous studies. See the following table:

	Zyban Group in Study AK1A4013 (n=204)	Placebo Group in Study AK1A4013 (n=200)	Zyban Group in Label-Dose Resp. Trial (n=461)	Placebo Group in Label-Dose Resp. trial (n=150)	Zyban Group in Label-Comp. trial (n=243)	Placebo Group in Label-Comp. Trial (n=159)
Insomnia	25%	12%	31%	21%	40%	18%
Nausea	8%	4%	N/A	N/A	9%	4%
Dry Mouth	6%	5%	11%	5%	10%	4%
Headache	7%	8%	N/A	N/A	N/A	N/A
Viral Infections	7%	7%	N/A	N/A	N/A	N/A
Flu Symptoms	1%	5%	N/A	N/A	N/A	N/A
Rashes	5%	5%	3%	<1%	4%	2%
Pruritis	2%	1%	3%	<1%	3%	1%
Urticaria	2%	0%	1%	0%	2%	0%

[Based on Sponsor's Label, Vol. 57.1, pp. 34-36, and Vol. 57.3, Listing 13, pp. 292-360.]

The AE profile was similar for ZYBAN and placebo. Fifty nine percent of the ZYBAN group and 52% of the placebo group experienced an AE during the Treatment phase. ZYBAN-treated subjects experienced more insomnia (25% vs. 12%), nausea (8% vs. 4%) and dry mouth (6% vs. 5%) than placebo-treated subjects, while placebo subjects experienced more headache (8% vs. 7%), viral infections (7% vs. 7%) and flu symptoms (5% vs. 1%) than ZYBAN-treated subjects. The frequency of AEs leading to discontinuation of study medication was similar for both groups: 7% for placebo; 6% for ZYBAN. Insomnia was the most frequently reported event leading to discontinuation of ZYBAN (2%), while headache was the most frequent event leading to discontinuation among the placebo group (2%). [Vol. 57.2, p.10.] These results were generally in line with the reports listed in the label from previous studies. The one notable exception was that the reports of dry mouth were 6% in this study (in the Zyban group) and 11% in the study listed in the label (in the Zyban group). [Vol. 57.1, pp. 34-36.]

While there is a risk from seizure at daily dosing levels in excess of 300mg/day, there were no reported cases of seizures during this trial. As Dr. Winchell mentioned in her review of November 15, 1996, "a seizure incidence of 1/1000 can be expected in the dose range used for smoking cessation, assuming precautions are taken to exclude patients with predisposition to seizure." The existing Warning section of the label discusses in bold the concern about the dose dependent risk of seizures. This reviewer feels that there is a need to continue to closely monitor for reports of seizures with this drug.

SECTION A SAFETY UPDATE

On August 25, 2000 the sponsor submitted a 120-Day Safety Update. The sponsor noted that there was no additional safety information to update the supplement. However, they will amend this supplement by submitting a final safety report on the Follow-up phase of Study AK1A4013 in November, 2000.

SECTION VII REVIEW OF PACKAGE INSERT

A copy of the sponsor's proposed draft labeling is attached (see Attachment II). It includes numerous changes most of that were previously submitted and are under separate review. There are 4 significant changes from the approved label that are directly related to this current supplement. These include a new paragraph and table of quit rates in the Clinical Trials section relating to patients with COPD, changes were also made to the Adverse Events section regarding the COPD trial, and changes in the Information to the Patient Section. The new paragraph and Table appear below and on the next page with this reviewer's deletions in strikethrough:

Use In Patients With Chronic Obstructive Pulmonary Disease (COPD):

[Draft

or]

APPEARS THIS WAY
ON ORIGINAL

Table 3: COPD Trial: Quit Rates by Treatment Group

Draft

- Reviewer's note: The narrative and tabular information on the "slips allowed" analysis in the Clinical Trials section relating to COPD patients should be deleted. This analysis was not based on the primary efficacy variable of "continuous quits". This information may make the label more confusing, harder to read, and not appreciably add to the information needed by physicians or patients.

Changes in the last paragraph of the **Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated with ZYBAN** appear below:

[

- Reviewer's Note: This statement appears to be adequate. The sentence from the previously approved label that was agreed to by the Agency states, "Adverse events were qualitatively and quantitatively similar to those observed in the dose-response and comparative trials." The results of the COPD trial are similar to the results obtained in the comparative and dose response studies.

Changes in the in the separate Patient Information leaflet provided for the patients, provide for the inclusion of a new question #3 as follows:

3. Can I take ZYBAN if I have mild to moderate chronic bronchitis and/or emphysema) also called chronic obstructive pulmonary disease or COPD)? Yes, ZYBAN combined with a behavior modification program has been shown to help people with COPD quit smoking. It is important to participate in the behavior program, counseling, or other support program your health care professional recommends.

- Reviewer's note: This statement appears to be adequate.

SECTION VIII CONCLUSIONS

- The efficacy and safety of Zyban, 300 mg/day given to patients with mild to moderate COPD, has been demonstrated in this clinical trial. The efficacy ratio, as compared to placebo, mimics the results in 2 earlier trials performed as part of the original NDA in a larger general population. However, in this latest trial the continuous quit rate was lower than in the previous trials. As a population, COPD patients are more resistant to smoking cessation therapies. This is most likely due to the difficulty in getting highly addicted smokers who feel the need to smoke despite their having mild to moderate COPD to accept smoking cessation therapies.

- The adverse events profile for this group of COPD patients appears to be very similar to that found in the general population.

- Post-marketing surveillance should closely monitor of the occurrence of seizures even at the currently recommended dosage of 300mg/day.

RECOMMENDATION

It is the opinion of this reviewer that this supplement NDA 20-711/SE1 #012 can be approved from a clinical standpoint provided the marked up proposed draft labeling is agreed
to by the sponsor and instituted.

SECTION IX APPENDIX

SECTION A. MATERIALS UTILIZED IN REVIEW

VOLUME	SUBMISSION DATE	MATERIAL
57.1	4-26-00	Index and labeling
57.2-57.11	4-26-00	Clinical data, statistical section, and CRFs
57.11	4-26-00	Literature references
57.12	4-26-00	CRFs

The Medical Officer reviews dated November 15, 1996, by Drs. Celia Winchell, and Chang Qing Li for the original Wellbutrin (Bupropion hydrochloride) Sustained Release NDA 20-711 were consulted during the course of this review.

/S/

Harold Blatt, D.D.S.
Clinical Reviewer

ATTACHMENT I

LITERATURE SEARCH

The sponsor performed a literature search for articles on the use of bupropion SR or nicotine replacement therapy in populations with COPD, emphysema, and chronic bronchitis. The following databases were searched through February 2000: Medline, Current Contents, and Eagle. The terms were covered were bupropion, nicotine replacement therapy, COPD, emphysema, chronic bronchitis, and the Lung Health Study. The sponsor mentions 28 references but only provided articles for 16 articles they felt were "key" to the submission. (Articles listed as "key" have an asterisk next to them.) No specific safety concerns were noted:

- Center for Communicable Diseases. Reducing the Health Consequences of Smoking: 25 Years in Progress. A Report of the Surgeon General. USDHHS, PHS, 1989; DHHS Publication no. (CDC) 89-8411.

- Morbidity and Mortality Weekly Reports, 42:645-648; 1993.

- Center for Communicable Diseases. Reducing the Health Consequences of Smoking: 25 Years in Progress. A Report of the Surgeon General. USDHHS, PHS, 1989; DHHS Publication no. (CDC) 89-8411.

- Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease, Respiratory Care and Critical Care Medicine, (Suppl), 152(5);1995.

- Hughes JA, Hutchinson DCS, Bellamy D, Dowd DE, et al. The influence of cigarette smoking and its withdrawal on the annual change of lung function in pulmonary emphysema, Quart. J Med, 202:115-124; 1982.

- *Anthonisen NR, Connett JE, Kiley JP, Altose MD, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1, JAMA, 272:1497-1505; 1994. The author's felt that an aggressive smoking intervention program significantly reduces the age-related decline in FEV_1 aged smokers with mild COPD. The use of an inhaled anticholinergic bronchodilator gives some small improvement in FEV_1 temporarily but does not influence the long-term decline of FEV.

- The Health Consequences of Smoking. Chronic Obstructive Lung Disease: a report of the Surgeon General. DHHS (PHS) 84-50205, US Govt. Printing Office, Washington, DC, 1984.

- Cosio M, Ghezzo MSC, Hogg JC, et al. The relations between structural changes in small airways and pulmonary functions tests. N Engl J Med 1978; 298:1277-81.

- Fletcher C, Peto R, Tinker, et al. The natural history of chronic bronchitis and emphysema. An eight-year study of early chronic obstructive lung disease in working men in London. New York: Oxford University Press. 1976; 70-105.

- Detels R, Tashkin DP, Simmons MS, Carmichael HE, Sayre JW, Rokaw SN, Coulson AH: The UCLA population studies of chronic obstructive respiratory disease. Agreement and disagreement of tests in identifying abnormal lung function. Chest 1982;82:630-638.

- *Gelb AF, Schein M, Kuei J, Tashkin DP, Muller NL, Epstein JD, Zamel N Limited contribution of emphysema in advanced chronic obstructive pulmonary disease. Am Rev Respir Dis. 1993; 103:1863-72. The authors felt that emphysema does not appear to be primarily responsible for expiratory airflow limitation in COPD.

- Fleiss JL, Statistical methods for rates and proportions, 2nd Edition. 1981. Wiley, New York.

- *Borron W, deBoisblanc BP. Pharmacotherapy of chronic obstructive pulmonary disease. J La State Med Soc. 1998; 150 (12): 596-600. The authors noted that, "nicotine substitution and the use of bupropion has been shown to double long-term smoking cessation success."

- *Lewis SF, Piasecki TM, Fiore MC, Anderson JE, Baker TB. Transdermal nicotine replacement for hospitalized patients: a randomized clinical trial. Preventive Medicine 1998; 27(2): 296-303. The authors noted that, "hospital interventions for smoking cessation may be most effective among patients hospitalized for a smoking related illness such as respiratory disease.

- *Roth MT, Westman EC. Safety of bupropion in patients with co-existing medical and/or psychiatric conditions. Pharmacotherapy 1999; 19(10): 1221. The authors concluded that bupropion appears safe for smoking cessation in patients with co-existing medical and psychiatric conditions. However, there should be monitoring in patients with underlying agitation, irritability, and mania.

- *Roth MT, Westman EC. Safety of Zyban in patients with co-existing medical and/or psychiatric conditions. J Invest Med Suppl. 1999; 47(2): 113A. Same comments as in previous article.

- Bailey WC, Ferguson GT, Higgins M, Hudson LD, et al. Strategies in preserving lung health and preventing COPD and associated diseases: The National Lung Health Education Program (NLHEP). Chest 1998; 113(2 Suppl.): 123S-163S.

- *Tonnesen P. Smoking cessation and prevention. Eur Respir Monogr 1998; 3(7): 127-134. The author note that bupropion was approved for smoking cessation, but at the time of the author's article, there was only 6 weeks outcome published and they were waiting for 1 year follow-ups and 1 or 2 confirmatory studies. The author also

noted the concern over seizures associated with bupropion. The author does not specifically discuss the use of bupropion in treatment of COPD patients but mention the use of NRT.

- *Petty TL, Nett LM. COPD: Why 'test your lungs, know your numbers' is the new battle cry. Consultant 1998; 38(10): 2501-2508. The authors suggest the use of sustained release bupropion for nicotine withdrawal symptoms. They also recommend the use of spirometry to detect early COPD.

- Fiore MC. How to prevent the progression of chronic bronchitis: the role of smoking cessation prevention. Monaldi Archives for Chest Disease 1994; 49(3 Suppl 1): 13-6.

- *Crowley TJ, Macdonald MJ, Walter MI. Behavioral anti-smoking trial in chronic obstructive pulmonary disease patients. Psychopharmacology 1995; 119: 193-204. The authors note that smoking causes COPD but the results of this behavioral trial, though statistically significant, do not provide a proven practical treatment for smoking in advanced COPD.

- *Buist AS, Sexton GJ, Nagy JM, Ross BB. The effect of smoking cessation and modification on lung function. Am Rev of Respir Dis. 1976; 114: 115-122. The authors found a "dramatic decrease in respiratory symptoms in those who stopped smoking, a moderate decrease in those who reduced their consumption by at least 25%, and very little change in those who did not appreciably modify their smoking consumption."

- *Kanner RE, Connett JE, Williams DE, Buist AS. Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: The lung health study. Am J of Med. 1999; 106(4): 410-416. In this prospective, randomized study using ITT analysis, smokers with early COPD who had smoking cessation intervention had fewer respiratory symptoms after a 5 year follow-up. However, no mention is made of the use of bupropion in this study.

- *Scanlon PD, Connett JE, Waller LA, Altose MD, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease - The Lung Health Study. Am J of Respir & Crit Care Med. 2000; 161(2): 381-390. In this prospective, randomized trial 3926 patients with mild to moderate COPD were studied. The authors concluded that, "smokers with airflow obstruction benefit from quitting despite previous heavy smoking, advanced age, poor baseline lung function or airway hyper-responsiveness." No mention is made of the use of bupropion.

- *Murray RP, Bailey WC, Daniels K, Bjornson WM, et al. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study Chest 1996; 109(2): 438-445. The authors concluded that nicotine polacrilex gum appears to be safe and unrelated to any cardiovascular illnesses or other serious side effects.

- *Murray RP, Anthonisen NR, Connett JE, Wise PA, et al. Effects of multiple attempts to quit smoking and relapses to smoking on pulmonary function. J of Clin Epidem. 1998; 51(12): 1317-1326. This study looked at 5887 patients with mild COPD and found that quitting smoking followed by relapse can still prevent some loss of lung function.

- *Nides MA, Rakos RF, Gonzales D, Murray RP, et al. Predictors of initial smoking cessation and relapse through the 1st 2 years of the Lung Health Study. J of Consul & Clin Psychology 1995; 63(1): 60-69. This study in COPD patients found the best predictor of relapse between 4 and 12 months to be smoking at least one cigarette between quit day and 4 months. Use of nicotine gum at 12 months predicted relapse in both males and females by 24 months. No mention is made of bupropion.

- *Kanner RE. Early intervention in chronic obstructive pulmonary disease -a review of the lung health study results. Med Clin of NAmer. 1996; 80(3): 523 ff. The lung health study found that, in patients with COPD, an effective smoking cessation program, can produce success rate of 20% (permanently give up smoking). The use of a bronchodilator only produces short-term improvement in FEV_1.

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In addition, this reviewer conducted a PUBMED search and found three additional articles. No new safety concerns were noted. The articles were as follows:

- Titlow K, et al. Drug coverage decisions: the role of dollars and values. Health Aff (Millwood). 2000 Mar-Apr.; 19(2):240-7. The authors noted that health insurers generally limit the use of Zyban by general exclusion or through restrictions on quantity or duration of use.

- Farnam, CR. Zyban: a new aid to smoking cessation treatment—will it work for psychiatric patients? J Psychosoc Nurs Ment Health Serv. 1999 Feb;37(2):36-42. Psychiatric patients who smoke are less successful at quitting and more prone to depression during the withdrawal. Changes in smoking status will affect the actions and side effects of neuroleptic medications. This is issue has been addressed in the revised draft labeling.

- Hebert S. Bupropion (Zyban, sustained-release tablets): reported adverse reactions. CMAJ 1999 Apr 6; 160(7): 1050-1. The article mentions 48 reports with 144 AEs. The most frequent were pruritis, urticaria, edema, tremors, dizziness, insomnia, and anxiety. Three cases of convulsions were reported. Convulsions are associated with larger than recommended Zyban dose of 300mg/day divided into 2 doses 8 hours apart. (ex. 600 mg/day).

ADDENDUM TO THE REVIEW

On November 20, 2000 the sponsor submitted an updated safety report to provide end-of-study safety information on Study AK1A4013 for the period from March 10, 2000 to August 16, 2000. This report showed that 2 additional patients discontinued during the treatment phase that was not previously reported. They were both lost to follow-up. One was from the Zyban group and one from the placebo group. The corrected total of discontinuations was 40 Zyban patients and 58 placebo patients. A Zyban treated subject (#5422) that was originally listed as having withdrawn consent has been reclassified as having withdrawn due to an adverse event (anxiety).

Discontinuations during the Follow-up Phase of the study were similar for placebo and active drug. The most common reason for withdrawal was being lost to follow-up with similar percentages in both groups. There were no new reports of serious adverse events (SAEs), deaths, or pregnancies.

The results of this updated safety report do not appear to provide any new information that would alter this reviewer's conclusions about this drug. Therefore I continue to believe that supplement NDA 20-711/SE1 #012 can be approved from a clinical standpoint provided the marked up proposed draft labeling is agreed to by the sponsor and instituted.

/S/

Harold Blatt, D.D.S.
Clinical Reviewer

MEMORANDUM TO THE FILE

DATE: October 16, 2000

APPLICATION NUMBER: NDA 20-711/SE8-012
Zyban (bupropion hydrochloride)

FROM: Judit Milstein, Regulatory Project Manager

TOPIC: 120 DAY SAFETY UPDATE

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120 day Safety Update submitted August 25, 2000
See M.O. Review, page 2