CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-711/SE8-012

Statistical Review(s)

Statistical Review and Evaluation

NDA 20-711, SE1-012
Name of drug: ZYBAN (Buproprion hydrochloride)
Applicant: Glaxo Wellcome
Indication: Smoking cessation in patients with COPD
Documents reviewed: Volumes 1-11, 17
Project manager: Judit Milstein
Clinical reviewer: Harold Blatt, D.D.S.
Dates: Letter date by sponsor—26 April 2000; date received by CDER—27 April 2000; user fee goal date—27 February 2001.

Reviewer: Stella Grosser

Introduction

Buproprion hydrochloride was originally developed as an anti-depressant (Wellbutrin) and approved in 1989 in an immediate release form and in a sustained release form in 1997. It was approved in 1997 as a sustained release tablet for smoking cessation under the name ZYBAN. This supplement is an application for the use of ZYBAN sustained release tablets as an aid to smoking cessation specifically among people with chronic obstructive pulmonary disease (COPD). It reports on a single study (AK1A4013) of patients with mild or moderate COPD, including emphysema, chronic bronchitis, or small airways disease.

Design

Study AK1A4013 is a multicenter, randomized, double-blind, parallel group study. Subjects were to receive either ZYBAN 150-mg once a day for the first three days and 150-mg twice a day, thereafter, or placebo through the 12-week treatment phase.

Four hundred and eleven patients were randomized and enrolled: 205 placebo group and 206 ZYBAN group. Of this population, 404 patients consumed at least one dose of study medication and and were included in the ITT population (200 placebo, 204 ZYBAN). Demographic information on these patients can be found in the medical officer's review. A per protocol population, defined as those subjects who took at least 28 days of treatment and who were 80% compliant over this time period, consisted of 325 patients (159 in the placebo and 166 in the ZYBAN group).

Efficacy

Primary Efficacy Evaluation

Measures

The primary efficacy measure calculated by the sponsor was the rate of continuous abstinence from week 4 through week 7 inclusive. Smoking abstinence was defined as subject self-report of not smoking and confirmed by expiratory carbon monoxide (CO) levels ≤ 10 ppm.

Because the period examined by the sponsor is in middle of the treatment phase, the clinical reviewers decided to emphasize instead the outcome from the end of the study, namely the continuous abstinence rate for weeks 9 through 12. The sponsor planned to calculate rates from this period as a secondary outcome. By design, therefore, confirmatory CO measurements were not taken at weeks 9 and 11 and so any continuity of smoking abstinence is based on self-report for those weeks.

Results

The rates of continuous abstinence from week 4 through week 7 inclusive in the ITT population were 28 % in the ZYBAN group and 16% in the placebo group. A Cochran-Mantel-Haenszel chi-square test for differences, controlling for investigator, yielded a significant p-value of 0.003. The rates of continuous abstinence from week 4 through week 7 inclusive in the per-protocol population were 34% in the ZYBAN group and 22% in the placebo group.

The rates of continuous abstinence from week 9 through week 12 inclusive in the ITT population were 22% in the ZYBAN group and 12% in the placebo group. The Cochran-Armitage chi-square test for differences yielded a significant p-value of 0.011. (Since rates for a variety of time periods were tested as a family simultaneously in the analysis of secondary outcomes, this p-value has been controlled for multiplicity using a stepdown permutation-resampling procedure that controlled for investigator).

Secondary Efficacy Evaluation

Measures

Numerous secondary efficacy outcomes were recorded for this study. They included 7-day abstinence rates at each weekly visit, number of cigarettes smoked per day, weight gain, and craving, withdrawal and depression symptoms (as measured by DSM-IV Severity of Nicotine Withdrawal questionnaire, University of Wisconsin Center for Tobacco Research and Intervention Craving and Withdrawal Scale (UWCTRI), and the Wisconsin Smoking Withdrawal Scale (WSWS)). In addition, the sponsor calculated a "slips allowed" quit rate, which is not considered in this review.

Results

Abstinence rates were consistently higher in the ZYBAN group than in the placebo group in both the ITT and per-protocol populations at every visit following week 1. In the ITT

populations, the rate peaked at about 35% in the ZYBAN group at week 4 and hovered around 30% by the end of the study, while rates in the placebo group were approximately 20% from week 3 until the end of the study.

Placebo-treated non-quitters tended to smoke slightly more than ZYBAN-treated non-quitters, though both groups cut their cigarette consumption by more than half by the end of the study. (Here non-quitters are the subjects who were not continuously abstinent during weeks 4 through 7.) Non-quitters in the placebo group decreased their consumption from a baseline mean of 27.3 cigarettes per day to approximately 12 per day after week 2, while ZYBAN non-quitters decreased from 27.8 cigarettes per day to approximately 10 per day.

For the most part, the two treatment groups were similar in results from the DSM-IV Severity of Nicotine Withdrawal questionnaire, UWCTRI and WSWS. ZYBAN-treated subjects had lower scores for Depressed Mood, Irritability-Frustration-or-Anger, Anxiety, and Difficulty Concentrating (DSM-IV Severity of Nicotine Withdrawal questionnaire), as well as Anger, Anxiety, Difficulty Concentrating, Sadness, Urge to Smoke, and Negative Affect (UWCTRI, WSWS).

Subgroup Analyses

The sponsor performed subgroup analyses on week 4 to 7 (mid-study) continuous abstinence rates. Rates for selected subgroups are shown in the table below. Female subjects had slightly lower abstinence rates overall than male subjects but relatively higher response to ZYBAN compared to placebo. Subjects 60 years of age or older had a higher overall abstinence rate with ZYBAN than subjects under 60. Small samples preclude meaningful analysis by race.

	Placebo	ZYBAN
Males	22/110 (20%)	34/112 (30%)
Females	10/90 (11%)	23/92 (25%)
Age < 60	19/138 (14%)	39/153 (25%)
Age ≥ 60	13/62 (21%)	18/51 (35%)

Analysis of end-of-study rates was not done for subgroups.

Conclusions

Whether judged by continuous total abstinence rates in weeks 4 through 7 (mid-treatment) or in weeks 9 through 12 (end of study), the chance of ceasing to smoke is statistically significantly higher for a subject with COPD taking ZYBAN than taking a placebo. These rates, 28% at mid-study and 22% at the end of the study in the the

ZYBAN group, are less than the comparable rates for subjects without COPD attempting smoking cessation by taking ZYBAN, 36% for all subjects at weeks 4-7 (review of NDA 20-711, Study 403, dated 14 Nov. 1996). A difference in this direction is expected, however, since people with COPD who nonetheless smoke are presumably more strongly addicted than other smokers.

/S/

Stella Grosser, Ph.D. 1/29/01
Mathematical Statistician

Concur: Thomas Permutt, Ph.D. /S/ 1/29/01
Mathematical Statistician (Team Leader)