

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-711 / S-015

Trade Name: Zyban

Generic Name: (bupropion hydrochloride)

Sponsor: GlaxoSmithKline

Approval Date: February 21, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-711 / S-015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-711 / S-015

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug
Administration
Rockville MD 20857

NDA 20-711/S-015

GlaxoSmithKline
P. O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Eric B. Benson
Director, Regulatory Affairs

Dear Mr. Benson:

Please refer to your supplemental new drug application dated May 24, 2001, received May 25, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyban (bupropion hydrochloride) extended-release tablets.

We acknowledge receipt of your submission dated October 12, 2001.

This supplemental new drug application provides for a revised carton for the 150 mg Advantage Pack-Trade and for revised labeling for the "Plan to Succeed Workbook" that incorporates and consolidates information from previous "Plan to Succeed Workbook", "Patient Program Guide", and "Zyban Q7A."

We have completed the review of this supplemental application, as amended, and it is approved effective on the date of this letter.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Judit Milstein, Regulatory Project Manager, at (301) 827-7440.

Sincerely

{See appended electronic signature page}

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Cynthia McCormick
2/21/02 12:23:01 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-711 / S-015

APPROVED LABELING

**ZYBAN® and
The ZYBAN Advantage Plan®
Plan to Succeed Workbook**
Unique Quitting Process. With Zyban you don't have to quit all at once.



Patients should set a date to stop smoking within the first 2 weeks of starting ZYBAN.

You and Your New Medication,
ZYBAN® (bupropion HCl) Sustained-Release Tablets

Your health care professional has prescribed ZYBAN as part of an overall program to help you quit smoking. ZYBAN is a non-nicotine, prescription medication to help you quit smoking.

You may have a few questions about your medication—how to take it the right way, what to expect, or the possibility of side effects and how to manage them. The answers to these and many other questions are provided in this brochure and in the "Information for the Patient" section printed at the end of this brochure. However, this is not meant as a substitute for professional advice. Be sure to discuss any questions you may have with your health care professional—he or she is your best source for more information.

IMPORTANT WARNINGS:
Seizure

There is a chance that approximately 1 out of every 1,000 people taking bupropion hydrochloride, the active ingredient in ZYBAN, will have a seizure. The chance of seizure is reduced by following

your health care professional's directions on how to take ZYBAN and discussing with your health care professional whether ZYBAN is right for you.

ZYBAN should not be used in combination with WELLBUTRIN® (bupropion hydrochloride) Tablets, WELLBUTRIN SR® (bupropion hydrochloride) Sustained-Release Tablets, WELLBUTRIN XL® (bupropion hydrochloride extended-release tablets), or any other medicines that contain bupropion hydrochloride. Combining ZYBAN with other products that contain bupropion greatly increases the chance of seizure.

Antidepressant Information

Although ZYBAN is not a treatment for depression, it contains the same active ingredient as the anti-depressant medications WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. Patients taking anti-depressants, and their families, should watch out for worsening depression or thoughts of suicide. Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated, panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and hyperactive, not being able to sleep, or other unusual changes in behavior. If this happens, especially at the beginning of treatment or after a change in dose, call your doctor. A patient Medication Guide will be provided to you with each prescription of ZYBAN entitled "About Using Antidepressants in Children and Teenagers." ZYBAN is not approved for use in children and teenagers.

It is important for you to know:

- The most common side effects with ZYBAN include dry mouth and difficulty sleeping.
- When used with a nicotine patch or alone, there is a risk of increased blood pressure, sometimes severe.
- To reduce the risk of serious side effects, tell your health care professional if you have liver or kidney problems.
- Let your health care professional know about any other prescription or over-the-counter medicines you are taking.
- ZYBAN is not recommended for women who are pregnant or breastfeeding.

You should not take ZYBAN if you:

- Have or have had a seizure disorder (for example, epilepsy).
- Have or have had an eating disorder (for example, bulimia or anorexia nervosa).
- Are abruptly discontinuing use of alcohol or sedatives (including benzodiazepines).
- Are already taking WELLBUTRIN®, WELLBUTRIN SR®, WELLBUTRIN XL®, or any other medicines that contain bupropion hydrochloride.
- Are currently taking or have recently taken a monoamine oxidase inhibitor (MAOI).
- Are allergic to bupropion hydrochloride.

You Can Succeed in Quitting

You have an important goal in your life—you want to quit smoking. You've made it this far. Congratulations!

Getting Started

- Step 1:* Get your prescription for ZYBAN (bupropion HCl) Sustained-Release Tablets filled, and start taking your ZYBAN as prescribed by your health care professional.
- Step 2:* Set a date to stop smoking (Quit Day) for 8 to 14 days after you've started taking ZYBAN.
- Step 3:* Read this brochure carefully.
- Step 4:* Start thinking of yourself as a nonsmoker.

Plan to Succeed

Whether this is your first time trying to quit smoking, or if you've tried many times before, you can succeed with help and support. People are much more likely to succeed in quitting when they know what obstacles they may face and have a plan to handle them.

Ready! You will review the reasons you want to quit now, and plan ways to cope with problems you expect to find while quitting.

Set! You will set your Quit Day, and make a plan to prepare yourself and others around you.

Go! You will plan for your first days as a nonsmoker, and help yourself stay on track for your future.

Ready!

You've probably already done some thinking about why you smoke, and why you want to quit. List the reasons you smoke. Be specific. Think about the way it makes you feel, the physical reasons, and the reasons that may have to do with your friends and family.

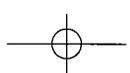
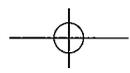
I smoke because:

1. _____

2. _____

3. _____

6



Now think about why you really want to quit now. Be as specific as you can.
I want to quit smoking because:

1. _____
2. _____
3. _____

"I've been smoking for 18 years. Started when I was a teenager. I tried to quit twice before, and even stayed off cigarettes for a couple of months one time. What's different for me now? Well, this time I know I'm really ready. I'm tired of smoking. It's not fun anymore, just a big hassle. My kids, my wife, everybody wants me to quit... And most importantly, I want myself to quit."

This section was prepared with the assistance of Michael Rice, MD, Director of the Center for Tobacco Research and Intervention at the University of Wisconsin Medical School, Madison, Wisconsin.

Planning for Triggers

When you know beforehand what may make you crave a cigarette, you can plan to deal with those difficult situations. If you know you're going to be in one of those trigger situations and you can't avoid it, plan for it ahead of time. Picture yourself in that situation as a nonsmoker.

For some people, triggers (✓) and suggestions for coping (*) are:

- ✓ Talking on the phone
 - ✓ Driving
 - ✓ Being around other smokers
 - ✓ Feeling tense or stressed
 - ✓ Making up in the morning
- * Try holding a straw or doodling
 - * Try chewing sugarless gum, or listening to books on tape
 - * Try staying in a smoke-free environment as much as possible, spending time with nonsmoking friends
 - * Try exercising, taking some deep breaths, or calling a friend
 - * Go for a first-thing-in-the-morning walk, or try changing the order of activities in the morning

1. My trigger is _____
and I will cope by _____

2. My trigger is _____
and I will cope by _____

3. My trigger is _____
and I will cope by _____

A Little Help from Your Friends

Quitting smoking is hard; there's no doubt about it. But it's made easier by talking to your family, friends and co-workers. Tell them you've resolved to quit now. Suggest ways they can help you:

"Be available to me for support when I need it, maybe just by phone for a little while each day."

"Help me get rid of all my cigarettes, ashtrays and other stuff at home, in the car, at work."

"Be positive and encouraging."

"Be patient with me as I go through this process."

Before Your Quit Day

Break the routines when you usually smoke a cigarette—drive a different way to work, listen to a different radio station, change the order of what you do in the morning.

Clean your home and get rid of ashtrays, matches, lighters, and ALL cigarettes. Do this the day before trash pick-up. Don't keep anything hidden away for an "emergency" or a "rainy day."

Have your car cleaned and deodorized so the smell doesn't make you want a cigarette.

Smoke with the hand you usually don't smoke with.

When you do smoke, go some place that's not comfortable or familiar.

Sell

Your Quit Day—

Your quit day is the date you will stop smoking completely. When picking your quit day, keep a few things in mind:

Don't set your quit day for what you know may be an unusually hard time—like when the relatives will be visiting or an important meeting or deadline is scheduled.

Consider picking a day that has special significance for you, such as a birthday, or special anniversary. Try to pick a day when you will be able to plan smoke-free activities.

My Quit Day is _____

Goal

On Your Quit Day:

Keep busy. Plan your activities.

Stay in nonsmoking areas as much as possible.

Call someone who is supporting you if you need encouragement.

Don't sit in your favorite chair—to avoid reminding yourself of where you often smoked.

"I'm working hard to get ready for quitting, in a way I never did before when I thought I could just stop. I'm writing things down, taking my medicine, talking to my doctor and friends who have quit... It seems like a lot of work before the real work starts! But I know that it will make it easier to beat this addiction and I'll have a better chance to quit for good this time."

Keep Going!

Refuse to give up. Quitting smoking is a process. It starts with deciding, continues with planning and adapting to being a new quitter, and moves on to maintaining yourself as a nonsmoker. First, change the way you think about smoking:

Take it one day, even one hour at a time. Don't worry about next month or next year; focus on right now.

Review your progress often and congratulate and reward yourself for what you've done.

Remind yourself that success is not based on willpower, but on good planning, support and a sincere commitment.

Accept that you are choosing not to smoke. You are in control, not cigarettes.

Remember that as each day goes by, your addiction gets weaker.

Remind yourself that just one cigarette can undo all your hard work.

Get plenty of rest and eat healthy.

Stressed About Stress?

There are many ways to manage your stress instead of reaching for a cigarette.

Take several slow, deep breaths.

Relax and take a 10-minute imaginary vacation.

Go for a walk or do some stretching exercises.

Stop and think about what's really bothering you. Will it matter a week from now?

Communicate your feelings; don't keep them bottled up.

Worried About Weight Control?

Many people who quit smoking worry about gaining weight. Most will gain less than 10 pounds. Most important, quitting smoking should be your first priority. If you do find the urge to munch to help control your urge to smoke:

Eat healthy snacks—try fruit, raw vegetables, sugarless mints or gum, or hard candies.

Drink lots of water to help yourself feel full.

Fit some physical fitness into your life. Go for walks, bike, exercise with a friend.

Try your best to eat a healthy, well-balanced diet.

Coping with Quitting

There are many ways to cope with symptoms you may experience when quitting. Consider the following list, and add your own.

Symptom

I will cope by...

If I crave nicotine or tobacco

- Brushing my teeth
- Doing some deep breathing
-

If I feel irritable

- Taking a few slow, deep breaths
- Soaking in a hot bath
-

If I have trouble sleeping

- Avoiding caffeine late in the afternoon and evening
- Calling my health care professional
-

If I have a hard time concentrating

- Taking a walk outside
- Making my schedule easier for a few days
-

If I am bothered by coughing or nasal drip

- Reminding myself that these "symptoms" are actually my body beginning to repair itself from the damage caused by smoking.

This Time is the Right Time

If you've tried to quit smoking before, you may be worried that you're headed for failure this time too. Don't let this feeling get in your way. Doing anything worthwhile is tough, and sometimes takes more than one try. When you have a realistic plan to fall back on, you are ready to prevent any setbacks—and to reach your goal!

Reward Yourself

Rewards are important and now that you are smoke-free, you need to find rewards that will bring you pleasure.

- Call a friend
- Buy something special
- Just take time for yourself



I plan to reward myself

For not smoking: I will reward myself by:

- On my quit day _____
- For 1 week _____
- For 2 weeks _____
- For 3 weeks _____
- For 1 month _____
- For 2 months _____
- For 3 months _____
- For 6 months _____

ZYBAN® (zi ban) (bupropion hydrochloride) Sustained-Release Tablets

Please read this information before you start taking ZYBAN. Also read this leaflet each time you renew your prescription, in case anything has changed. This information is not intended to take the place of discussions between you and your doctor. You and your doctor should discuss ZYBAN as part of your plan to stop smoking. Your doctor has prescribed ZYBAN for your use only. Do not let anyone else use your ZYBAN.

IMPORTANT WARNING:

There is a chance that approximately 1 out of every 1,000 people taking bupropion hydrochloride, the active ingredient in ZYBAN, will have a seizure. The chance of this happening increases if you:

- have or have had a seizure disorder (for example, epilepsy);
- have or have had an eating disorder (for example, bulimia or anorexia nervosa);
- are abruptly discontinuing use of alcohol or sedatives (including benzodiazepines);
- take more than the recommended amount of ZYBAN; or
- take other medicines with the same active ingredient that is in ZYBAN, such as WELLBUTRIN® (bupropion hydrochloride) Tablets, WELLBUTRIN SR® (bupropion hydrochloride) Sustained-Release Tablets, and WELLBUTRIN XL® (bupropion hydrochloride extended-release tablets). (These medicines are used to treat depression.)

You can reduce the chance of experiencing a seizure by following your doctor's directions on how to take ZYBAN. If you experience a seizure while taking ZYBAN, stop taking the tablets immediately, contact your doctor, and do not restart ZYBAN. In addition, tell your doctor if you have or have had other medical conditions. You should also discuss with your doctor whether ZYBAN is right for you.

Important Information I should know and share with my family about taking antidepressants.

Although ZYBAN is not a treatment for depression, it contains the same active ingredient as the antidepressant medications WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL. Therefore, you should be aware of the following information. Patients

taking antidepressants, and their families, should watch out for worsening depression or thoughts of suicide. Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated, panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and hyperactive, not being able to sleep, or other unusual changes in behavior. If this happens, especially at the beginning of antidepressant treatment or after a change in dose, call your doctor. A patient Medication Guide will be provided to you with each prescription of ZYBAN entitled "About Using Antidepressants in Children and Teenagers." ZYBAN is not approved for use in children and teenagers.

1. What is ZYBAN?

ZYBAN is a prescription medicine to help people quit smoking. Studies have shown that more than one third of people quit smoking for at least 1 month while taking ZYBAN and participating in a patient support program. For many patients, ZYBAN reduces withdrawal symptoms and the urge to smoke. ZYBAN should be used with a patient support program. It is important to participate in the behavioral program, counseling, or other support program your health care professional recommends.

2. Who should not take ZYBAN?

You should not take ZYBAN if you:

- have or have had a seizure disorder (for example, epilepsy);
- are already taking WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, or any other medicines that contain bupropion hydrochloride;
- have or have had an eating disorder (for example, bulimia or anorexia nervosa);
- are abruptly discontinuing use of alcohol or sedatives (including benzodiazepines);
- are currently taking or have recently taken a monoamine oxidase inhibitor (MAOI); or
- are allergic to bupropion.

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.

4. Are there special concerns for women?

ZYBAN is not recommended for women who are pregnant or breastfeeding. Women should notify their doctor if they become pregnant or intend to become pregnant while taking ZYBAN.

5. Are there any concerns for patients with liver or kidney problems?

If you have liver or kidney problems, tell your doctor before taking ZYBAN. Depending on the severity of your condition, your doctor may need to adjust your dosage.

6. How should I take ZYBAN?

You should take ZYBAN as directed by your doctor. The usual recommended dosing is to take one 150-mg tablet in the morning for the first 3 days. On the fourth day, begin taking one 150-mg tablet in the morning and one 150-mg tablet in the early evening. Doses should be taken at least 8 hours apart.

• **Never take an "extra" dose of ZYBAN.** If you forget to take a dose, do not take an extra tablet to "catch up" for the dose you forgot. Wait and take your next tablet at the regular time. Do not take more tablets than your doctor prescribed. This is important so you do not increase your chance of having a seizure.

• It is important to swallow ZYBAN Tablets whole. Do not chew, divide, or crush tablets.

7. How long should I take ZYBAN?

Most people should take ZYBAN for at least 7 to 12 weeks. Some people may need to take ZYBAN for a longer period of time to assist in their smoking cessation efforts. Follow your doctor's instructions.

8. When should I stop smoking?

It takes about 1 week for ZYBAN to reach the right levels in your body to be effective. So, to maximize your chance of quitting, you should not stop smoking until you have been taking ZYBAN for 1 week. You should set a date to stop smoking during the second week you're taking ZYBAN.

9. Can I smoke while taking ZYBAN?

It is not physically dangerous to smoke and use ZYBAN at the same time. However, continuing to smoke after the date you set to stop smoking will seriously reduce your chance of breaking your smoking habit.

10. Can ZYBAN be used at the same time as nicotine patches?

Yes, ZYBAN and nicotine patches can be used at the same time but should only be used together under the supervision of your doctor. Using ZYBAN and nicotine patches together may raise your blood pressure, sometimes severely. Tell your doctor if you are planning to use nicotine replacement therapy because your doctor will probably want to check your blood pressure regularly to make sure that it stays within acceptable levels.

DO NOT SMOKE AT ANY TIME if you are using a nicotine patch or any other nicotine product along with ZYBAN. It is possible to get too much nicotine and have serious side effects.

11. What are possible side effects of ZYBAN?

Like all medicines, ZYBAN may cause side effects. Do not rely on this summary alone for information about side effects. Your doctor can discuss with you a more complete list of side effects that may be relevant to you.

- Hypertension (high blood pressure). In some cases severe, has been reported in patients taking ZYBAN alone and in combination with nicotine replacement therapy (for example, a nicotine patch, see Question #10).
- The most common side effects include dry mouth and difficulty sleeping. These side effects are generally mild and often disappear after a few weeks. If you have difficulty sleeping, avoid taking your medicine too close to bedtime.
- The most common side effects that caused people to stop taking ZYBAN during clinical studies were shakiness and skin rash. Stop taking ZYBAN and contact your doctor or health care professional if you have signs of an allergic reaction such as a rash, hives, or difficulty in breathing. It is not possible to predict whether a mild rash will develop into a more serious reaction. Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor immediately, since these symptoms may be the first signs of a serious reaction. Discuss any other troublesome side effects with your doctor.
- Use caution before driving a car or operating complex, hazardous machinery until you know if ZYBAN affects your ability to perform these tasks.

12. Can I drink alcohol while I am taking ZYBAN?

It is best to not drink alcohol at all or to drink very little while taking ZYBAN. If you drink a lot of alcohol and suddenly stop, you may increase your chance of having a seizure. Some people have reported lower alcohol tolerance during treatment with ZYBAN. Therefore, it is important to discuss your use of alcohol with your doctor before you begin taking ZYBAN.

13. Will ZYBAN affect other medicines I am taking?

ZYBAN may affect other medicines you're taking. It is important not to take medicines that may increase the chance for you to have a seizure. Therefore, you should make sure that your doctor knows about all medicines—prescription or over-the-counter—you are taking or plan to take.

14. Do ZYBAN Tablets have a characteristic odor?

ZYBAN Tablets may have a characteristic odor. If present, this odor is normal.

15. How should I store ZYBAN?

- Store ZYBAN at room temperature, out of direct sunlight.
- Keep ZYBAN in a tightly closed container.
- Keep ZYBAN out of the reach of children.

This summary provides important information about ZYBAN. This summary cannot replace the more detailed information that you need from your doctor. If you have any questions or concerns about either ZYBAN or smoking cessation, talk to your doctor or other health care professional.

This is your personal contract. Tear it out of your workbook and post it on your refrigerator.

I resolve to quit smoking on _____.

As part of my plan for success, I will take my medication, follow the plan prescribed by my health care professional and work hard to achieve my goal.

My three most important reasons for quitting are:

1. _____

2. _____

3. _____

signature _____ *date*

witness _____ *date*





GlaxoSmithKline
Research Triangle Park, NC 27709
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A012282

January 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-711 / S-015

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE

Division of Anesthetic, Critical Care, and Addiction Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-711

Name of Drug: Zyban (bupropion hydrochloride) Sustained-Release Tablets

Sponsor: GlaxoSmithKline

Material Reviewed

Submission Date(s): May 24, 2001 (S-015), October 12, 2001 (S-015/BL)

Receipt Date(s): May 25, 2001 (S-015), October 15, 2001 (S-015BL)

Background and Summary Description: This supplement proposed revisions to the final printed label for the ancillary material. S-015 was compared to the material submitted on June 18, 1997, which was found acceptable (letter dated March 14, 2001).

S-015 provides for revised labeling for the "Carton for the 150 mg Advantage Pack-Trade" and revised labeling for the "Plan to Succeed Workbook" which consolidates information from the previous "Plan to Succeed Workbook," "Patient Program Guide," and "Zyban Q&A." The dosing calendar, magnet, pen will not be included in ZYBAN Advantage Pack.

S-015BL provides for further reduction of the size of the packaging.

It should be noted that the submission on June 18, 1997 did not include any material for the 100 mg dosage form because this strength was not going to be marketed at that time.

Status Report

Reviews Completed: Sara E. Shepherd, RPM, February 6, 2001
Laura Governale, DDMAC, November 29, 2001 (date of review)

Reviews Pending: none

RPM Review

ZYBAN Advantage Pack Carton-

The title changed from "ZYBAN Advantage Plan" to "ZYBAN Advantage Pack."
Wording has been moved to accommodate the smaller package.
Removed the section entitled "What you'll find in this ZYBAN Advantage Pack"

Plan to Succeed Workbook-

Consolidates information from the previous "Plan to Succeed Workbook," Patient Program Guide," and "Zyban Q&A." See information attached below.

There were only minor revisions between the May 24, 2001 submission and the October 12, 2001 submission. Page 8 was reformatted ("Planning for Triggers").

The "Information for the Patient" was attached to the end of the workbook.
The material submitted on June 18, 1997, which was found acceptable (letter dated March 14, 2001), was compared to the "Information for the Patient" attached to the workbook.

In the "IMPORTANT WARNING" section, the following was added.

[

A new section was added "Section 3. Can I take ZYBAN if I have mild-to-moderate chronic and/or emphysema (also called chronic obstructive pulmonary disease or COPD)?"

A new section was added "Section 5 Are there any concerns for patients with liver or kidney problems?"

In section 10 (formerly Section 8) "Can ZYBAN be used at the same time as nicotine patches?" the following was added.

"..... may raise your blood pressure, sometimes severely. Tell your doctor if you are planning to use nicotine replacement therapy because your doctor will probably want to check your blood pressure regularly to make sure that it stays within acceptable levels."

In section 11 (formerly Section 9) “What are the possible side effects of ZYBAN?” the following information was added/modified.

“.....Do not rely on this summary alone for information about side effects. Your doctor can discuss with you a more complete list of side effects that may be relevant to you.”

“Hypertension (high blood pressure) in some cases severe, has been reported in patients taking ZYBAN alone and in combination with nicotine replacement therapy (for example, a nicotine patch, see Question #10).”

“Stop taking ZYBAN and contact your doctor or health care professional if you have signs of an allergic reaction such as a rash, hives, or difficulty breathing. It is not possible to predict whether a mild rash will develop into a more serious reaction. Therefore if you experience a skin rash, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor immediately, since these symptoms may be the first signs of a serious reaction. Discuss any troublesome side effects with your doctor.”

Recommendations

DDMAC did not have any comments to forward to the Sponsor. This submission, as amended, should be approved.

Sara E. Shepherd/ Regulatory Project Manager

Parind Jani/Supervisory Comment/Concurrence

WITHHOLD 18 PAGE(S)

Draft Labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Judit Milstein
2/21/02 11:13:36 AM
CSO

Celia Winchell
2/21/02 11:18:10 AM
MEDICAL OFFICER
I concur with the project manager's review and have
no objections to the proposed changes. No separate
medical officer review was prepared for this supplement.

Parinda Jani
2/21/02 11:28:43 AM
CSO



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS
HFD-42, Room 17B-17, 5600 Fishers Lane, Rockville MD 20857

Tel:(301) 827-2831

CSO Review and Evaluation of Labeling

NDA #:	20-711/SLR-015
Drug Name (generic):	Zyban® (bupropion hydrochloride) Sustained-Release Tablets
Sponsor:	GlaxoSmithKline
Indication:	Aid to smoking cessation treatment
Type of Submission:	Supplemental Labeling Application
Date of Submission:	May 24, 2001; October 12, 2001
Date of Receipt (CDR):	May 25, 2001; October 15, 2001
Date of Review:	November 19, 2001
Material Reviewed:	Zyban® Plan to Succeed Workbook and Zyban® Advantage Pack Carton
Reviewer:	Laura Governale, Pharm.D.
Project Manager:	Judit Milstein

1 Background

The sponsor submitted a proposal to revise the carton labeling and the patient information booklet entitled, "Plan to Succeed Workbook." The submission dated May 24, 2001, reduces the dimensions of the carton and consolidates the information from the previous "Plan to Succeed Workbook," "Patient Program Guide," and "ZYBAN Q&A" into one format. The submission

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2 Summary of the Sponsor's Rationale for Consolidating the "Plan to Succeed Workbook"

The Sponsor states that only 8% or 81,000 patients receiving a new prescription for Zyban enrolled in the ZYBAN Advantage Plan. The consolidation of the workbook is intended to increase the use of the ZYBAN behavior modification materials by simplifying use and encouraging self-directed use of the plan. The booklet will also refer the patients to the www.ZYBAN.com and www.Ibreathe.com web sites for further information on smoking cessation.

3 Reviewer's Comments

The sponsor's plan appears to be a cost cutting measure rather than an effort to reach more patients. Warning statements in the patient information booklet appear to be adequately addressed and Reduction of the carton dimension may also allow pharmacy shelves to stock more of the product and possibly increase sales by increasing inventory and reducing stock-outs. While the terms "Advantage" and "Unique Quitting Process" may sound like a superiority claim in nature, these terms have been used for this product for the past 3 years. It can also be argued that Zyban is different from other smoking cessation aids which primarily work through nicotine replacement. This reviewer finds no objections to the use of these terms at this time.

RECOMMENDATIONS: Labeling revisions may proceed.

Laura Governale, Pharm.D.
Regulatory Review Officer

Date

Spencer Salis, Pharm.D.
Branch Chief

Date

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/s/

Laura Governale
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CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): Drug Marketing, Advertising and Communications HFD-40			FROM: Cynthia G. McCormick Division of Anesthetic, Critical Care and Addiction Drug Products HFD-170		
DATE October 23, 2001	IND NO.	NDA NO 20-711/s-017	TYPE OF DOCUMENT Labeling supplement	DATE OF DOCUMENT October 12, 2001	
NAME OF DRUG Zyban (bupropion hydrochloride)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE November 30, 2001	
NAME OF FIRM: GlaxoSmithKline					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
<p>COMMENTS/SPECIAL INSTRUCTIONS: On May 24, 2001, the sponsor submitted Supplement S-015, that provides for revisions to the Zyban Advantage Plan and Zyban Advantage Pack. On October 12, 2001, the sponsor submitted an amendment to the original supplement, describing changes in the format and size of the labeling.</p> <p>The original submission dated May 24, 2001 is submitted with this consult. Please, return the blue jacket to Judit Milstein Desk copy of the October 12, 2001, is also submitted with this consult.</p> <p><u>We request recommendation on approvability</u></p> <p>Cc: al responses to Judit Milstein (milsteinj at 7-7440, and Aleta Crane (cranea)</p>					
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

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/s/

Judit Milstein
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NDA 20-711/S-015
SUPPLEMENT

PRIOR APPROVAL

Glaxo Welcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Eric B Benson
Director, Regulatory Affairs

Dear Mr. Benson:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Zyban® (bupropion hydrochloride)
NDA Number:	20-711
Supplement number:	S-015
Date of supplement:	May 24, 2001
Date of receipt:	May 25, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 24, 2001, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and
Addiction Drug Products HFD-170
Attention: Division Document Room, 9B23
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me at (301) 827-7410.

Sincerely yours,

Judit Milstein
Regulatory Project Manager
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Judith Milstein
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