CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-711

CORRESPONDENCE

INCOMING
APR 1997

Memorandum

DATE: April 2, 1997

TO: Tom ~~Laughren~~ Paul Leber

FROM: Celia Winchell

RE: Labeling for Zyban (bupropion H Cl Sustained Release)

CC: Curtis Wright

Bonnie McNeal

Thanks for agreeing to take a look at the labeling for Zyban to ensure it does not conflict importantly with the labeling for Wellbutrin SR. This is the version agreed upon with Glaxo today.

Significant points of departure from Wellbutrin SR labeling are:

MEETING MINUTES

Meeting Date: May 14, 1997 Location: Parklawn 13B-45

NDA/DRUG: NDA 20-711/Zyban for Smoking Cessation

Type of Meeting: Requested by Office Director to Discuss the Application

Attendees:
Dr. Paula Botstein, Director ODE III
Dr. Curtis Wright, Acting Division Director
Dr. Chang Qing Li, Medical Reviewer
Dr. Celia Winchell, Primary Medical Reviewer
Corinne Moody, Chief, Project Management Staff
Bonnie McNeal, Project Manager

Concerning the risk of seizures with this drug, the division pointed out that this drug had been taken to the advisory committee. There was a good discussion there. They said that nicotine could not be used in certain patients, such as those with wound healing issues. Also, they said as clinicans, they did not want this drug to be used off label. Even though there is a seizure risk with this product, the committee felt it would be of benefit since smoking is a major addiction and health risk.

There was a lengthy discussion about allergic reactions seen with Zyban. The division had asked the sponsor to pull together all allergic reactions in the Safety Update which they submitted to the division. In all trials with Zyban under review for smoking cessation, there were about 6 serious allergic reactions in about 1800 patients. It was agreed to change the wording in the PRECAUTIONS: General section of the package insert to read as follows:

Filename: wellmtg6.wpd
Edited by Celia Winchell; Corinne Moody
Final prepared 8/11/97

cc: NDA 20-711
Div. Files
HFD-170/McNeal/CWinchell/Li/CWright/Moody
HFD-003/PBotstein

MEETING MINUTES

Meeting Date: October 8, 1996 Time: 1:00pm Location: Parklawn 9B-45

NDA/DRUG: NDA 20-711/Wellbutrin SR for Smoking Cessation

External Participant: Glaxo Wellcome Inc.

Type of Meeting: Face-to-face to Prepare for Drug Abuse Advisory Committee (DAAC) Meeting

FDA Attendees:
Dr. Celia Winchell, Primary Medical Reviewer
Dr. BeLinda Hayes, Pharmacology and Abuse Liability Reviewer
Dr. Tom Permutt, Supervisory Statistician
Dr. Jonathan Ma, Statistical Reviewer
Peter Lockwood, Pharmacokinetics Reviewer
Dr. Curtis Wright, Acting Division Director
Dr. Monte Scheinbaum, Secondary Medical Reviewer
Bonnie McNeal, Project Manager

External Attendees:
Eric Benson, Regulatory Affairs
Jim Murray, Regulatory Affairs
Joseph DeVeaugh-Geiss, Clinical Research
Sharyn Batey, Medical Affairs

The sponsor started by presenting results of the 405 study. They stated that this could have an impact on where the drug will be placed in the armamentarium of smoking cessation products. The results show the quit rates for placebo of 23%, for Habitrol alone as 36%, Wellbutrin SR alone 49%, and Wellbutrin SR plus Habitrol of 58%. Significant differences were found between Habitrol and Habitrol plus Wellbutrin groups, and between Habitrol and Wellbutrin groups.

The sponsor was asked if they would propose the combination as a firstline treatment. The sponsor said not at this time but that it is an option that may be appropriate for some patients.

The sponsor presented adverse events from the 405 study. Some of those were 2 rash, 1 urticaria, 1 meningitis and 1 chest pain. There was a discussion of anaphylactic reactions which are rare.

There was a discussion about presenting the 405 study to the DAAC. The agency said they would have to review it first. The sponsor felt that the data should be presented to give the

committee the whole picture of the drug. The agency said the abstinence data would be most important for the committee to see. The craving data is harder to evaluate.

The issue of seizures with this drug was discussed. So far the smoking cessation products have tolerated few serious side effects. There is a 6000 patient data base now, so one can evalute the seizure risk with this product. The sponsor said there was a similar issue in the 1980's when Wellbutrin was coming out on the market as a non-tricyclic antidepressant. The warning about seizures is on the label. The agency said that the DAAC will need to be convinced that the drug has an adequate risk/benefit ratio.

The agency suggested the sponsor make a one hour presentation to the DAAC. Fifteen (15) minutes would be on efficacy in the 3 pivotal studies including a mention of the dropouts. The efficacy of study 405 could be presented, concerning abstinence, with a backup slide on withdrawal, craving, and adverse events. Thirty (30) minutes could be on the safety of bupropion, with experience in depression, history of seizures, allergic reactions, and the doses that should be used in smoking cessation. Then 15 minutes could be to discuss the proposed labeling and 15 minutes for questions.

The DAAC sessions were proposed by the agency according to the following schedule:

I) Sponsor presents safety, efficacy and precautionary information in the label for about 40 minutes.
FDA medical reviewer responds.
Three questions are presented to the committee
a) Is the drug effective?
b) Is the drug safe?
c) Is it approvable?

II) Agency presents arguments for role of drug as a first-line or second-line drug with a discussion of the risk/benefit ratio for 10 minutes.
Sponsor responds about 10 min.

III) Sponsor presents argument for name change, about 5 minutes.
FDA responds about 5 minutes.
Committee responds to last two issues.

The sponsor asked if they could claim in the label that Wellbutrin SR is better than Habitrol. The agency replied that there must be two adequate and well controlled trials to do this. The agency added that if the sponsor wanted to say it was better than "nicotine replacement", that they should use more than one product.

The sponsor will send in their briefing package for the committee about November 1, 1996 so that the division can review it.

Signature, minutes preparer: Bonnie McNeal 5/29/97

Filename: wellmtg4.wpd
Edited by Corinne Moody; Celia Winchell; BeLinda Hayes; Tom Permutt; Jonathan Ma; Monte Scheinbaum
Final prepared 8/11/97

cc: NDA 20-711
Div. Files
HFD-170/McNeal/BHayes/TPermutt/CWinchell/JMa
HFD-170/MScheinbaum/CWright/CMoody

MEETING MINUTES

MEETING TYPE: Team Meeting - Preparation for December Advisory Committee

NDA/DRUG: NDA 20-711/Wellbutrin SR

SPONSOR: Glaxo Wellcome Inc.

DATE: September 25, 1996

ATTENDEES: Celia Winchell
Peter Lockwood
Pat Maturu
Lucy Jean
Jack Longmire
Tom Permutt
Curtis Wright
Bonnie McNeal

Medical reviews on Studies 401, 402 and 403 are finished.

The package for the advisory committee (AC) must be prepared by the end of October. The safety and approvability of this indication need to be presented. We need data on the pivotal trials and an integrated summary of safety or a special safety review on seizures.

We need to ask the committee does the product work, is it safe and how should we label it? We also need to send the question of the name change to the AC. If we can review the 405 study before the meeting, the sponsor can present it to the AC. The issue here is safety, not efficacy and how to use bupropion with a nicotine patch.

The questions for the committee will be:

1) Is there substantial evidence for the efficacy of bupropion in smoking cessation? Is there substantial evidence for the safety of bupropion in smoking cessation?

2) What is the opinion of the committee regarding special restrictions with this drug? Should it be a first-line or second-line drug?

3) Does the committee have objections to the sponsor marketing the drug with a new tradename for the new indication of smoking cessation?

4) A discussion of the labeling is needed.

The package for the AC member needs the following:

1) Medical reviews, the 3 trials, integrated summary of safety and efficacy and a preliminary review of study 405

2) Stats review

3) Abuse liability issues from pharmacologist

4) Pharmacokinetics review

5) The label after it is finalized with the company

The specific agenda for the AC meeting:
Open Public Session - ½ hour
Sponsor Presents - 1 hour (we meet with them to discuss what)
Medical Officer Presents - 15 min., brief pivotal trials and overview of general safety
Break
Special Topics: Seizure Risks and Name Change- 30-60 min.
Sponsor Response
Ask Committee to consider first 3 questions
Break for Lunch
Ask Committee to consider the last question

Filename: wellmtg3.wpd
Edited by CWinchell; Lucy Jean; Pat Maturu; Jack Longmire; Tom Permutt
Final prepared 8/11/97.

cc: NDA 20-711
Div. Files
HFD-170/McNeal/LJean/PMaturu/JLongmire/TPermutt/CWinchell

MEETING MINUTES

MEETING TYPE: Team Meeting - Progress of NDA

NDA/DRUG: NDA 20-711/Wellbutrin SR

SPONSOR: Glaxo Wellcome Inc.

DATE: September 11, 1996

ATTENDEES: Celia Winchell
BeLinda Hayes
Jonathan Ma
Monte Scheinbaum
Peter Lockwood
Pat Maturu
Bonnie McNeal

Medical: Review on Study 403 is finished. Study 402 is 80% done. Celia is awaiting the submission of Study 405 in October. Then she can review that study and prepare the integrated summary of safety.

Review of the proposal to change the name of the drug for marketing as a smoking cessation product has been done. Many products are labeled under different names. The company gave four arguments for making the change:
1. It will be marketed jointly with a self-help package (we need to find out what the response rate is to another product with a similar strategy (Nicoderm for example-check with Lorrie Stewart or Mary Lambert).
2. People using it will be stigmatized for using an antidepressant medication.
3. Reimbursement issues may be simplified for patients in managed care plans.
4. Sponsor thinks it can be labeled safely. Another drug, Cardura is used for hypertension and benign prostatic hyperplasia (BPH). Another product is Rogaine which is used for baldness and also for hypertension.
This proposal needs to go to the Labeling and Nomenclature Committee.

The pattern of seizures in Wellbutrin SR did not change from the immediate release formulation. Seizures occurred at steady-state. We can keep the same seizure warning as in the previous label.

Pharmacology: It will take about one month to finish. Pharmacology done, toxicology needs to be finished. It was noted that the dependence portion of the label needs to be rewritten.

Pharmacokinetics: Need about one month to finish. There are two PK studies which were

not submitted to the NDA in Neuropharm.

This product must go to the DAAC because it is the first non-Nicotine product to be introduced for smoking cessation. It may go in December or February.

Chemistry: Review awaiting responses from sponsor on standards for the drug substance, EER and EA.

Statistics: Will need telecon on questions to Basil Sumatra.

Filename: wellmtg2.wpd
Edited by Celia Winchell; BeLinda Hayes; Jonathan Ma; Monte Scheinbaum; Pat Maturu; Corinne Moody
Final prepared 8/11/97

cc: NDA 20-711
Div. Files
HFD-170/McNeal/CWinchell/BHayes/JMa/MScheinbaum
HFD-170/PMaturu/CMoody

MEETING MINUTES

MEETING TYPE: NDA Filing Meeting

NDA/DRUG: NDA 20-711/Wellbutrin SR for Smoking Cessation

SPONSOR: Glaxo Wellcome Inc.

DATE: July 15, 1996

ATTENDEES:
Curtis Wright
Celia Winchell
BeLinda Hayes
Peter Lockwood
Dale Conner
Jonathan Ma
Monte Scheinbaum
Diane Shnitzler
Abi D'Sa
Pat Maturu
Bonnie McNeal

Medical: Celia Winchell said the NDA looks ok for filing medically. The pivotal trials are 402, 403 and 405. The last, 405, will be submitted in October. Studies 402 and 403 are pivotal trials. The largest centers are in studies 403 and 405.

Pharmacokinetics: The kinetics are well delineated with three additional studies. No audits are necessary since the studies have already been accepted by HFD-120.

Chemistry: The application is fileable, though there will be some issues to solve before approval.

Pharmacology: There are not pharm/tox issues. Will have to look into the reproductive/tox profile for this product.

Statistics: No statistical issues. The drug is not efficacious under 300 mg. From 450-600 mg the incidence of seizures is too high. The drug will be contraindicated in seizure and eating disorders.

The sponsor wants a name change. They state there is a stigma to taking an antidepressant. A new name means a new label that could be linked to a self-help program. Will take the name change to the Nomenclature Committee. The agency is not sympathetic to a name change unless it will improve safety or prevent confusion or overdose.

The team was reminded that they could use the reviews from HFD-120. If they were done well, there is no reason to redo them.

The drug has risks that nicotine doesn't have. There is a low therapeutic index. As the first non-nicotine product it will have to go to the advisory committee.

Filename: wellfile.mtg
Edited by Celia Winchell; BeLinda Hayes; Jonathan Ma; Monte Scheinbaum; Abi D'Sa; Pat Maturu
Final prepared 8/11/97

cc: **NDA 20-711**
Div. Files
HFD-170/McNeal/CWinchell/BHayes/DConner/CWright
HFD-170/JMa/MScheinbaum/AD'Sa/PMaturu/CMoody

MEETING MINUTES

MEETING TYPE: Sponsor Delivered Electronic Files

NDA/DRUG: NDA 20-711/Wellbutrin SR

SPONSOR: Glaxo Wellcome Inc.

DATE: June 18, 1996

ATTENDEES:	Celia Winchell	
	Jonathan Ma	
	Tom Permutt	
	Bonnie McNeal	of HFD-170/CDER/FDA
and	Eric Benson	
	Dr. Andy Johnston	of Glaxo Wellcome

The sponsor delivered electronic files to the review division on the new NDA.

The medical and statistical reviewers reported that they had all of the information which they requested. The medical reviewer asked for the final study reports on electronic disk.

The sponsor was informed that we will not take the product to the advisory committee in August but will do so at a later date. The sponsor asked why an advisory committee meeting was necessary. They were told that treatment for smoking has traditionally produced very few adverse events. This drug (bupropion) has some risk of adverse events. We must answer the question of whether we want to expose patients to a non-nicotine treatment. Also, how will the product be used, as a nicotine replacement product or as an adjunct to nicotine replacement. Also, the commissioner is very interested in nicotine replacement products.

Filename: wellmtg1.wpd
Edited by Celia Winchell; Jonathan Ma; Tom Permutt
Final prepared 8/11/97

cc: NDA 20-711
Div. Files
HFD-170/McNeal/Winchell/Permutt