CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-190

Administrative Documents

NDA 21-190
BuSpar®
(buspirone hydrochloride)
Capsules

TABLE OF CONTENTS

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-190 /SE____ - ____

Drug BuSpar® Capsules Applicant Bristol-Myers Squibb Co.

RPM Anna Marie Honnonay Phone 594-5535

☑505(b)(1)
☐505(b)(2) Reference listed drug ____

☐Fast Track ☐Rolling Review Review priority: ☑S ☐P

Pivotal IND(s) 8,705

Application classifications:
Chem Class ____
Other (e.g., orphan, OTC) ____

PDUFA Goal Dates:
Primary 12/22/00
Secondary ____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☑User Fee Paid $ 136,141
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☑AP ☐ AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... ____
  Original proposed labeling (package insert, patient package insert) ..... ✓
  Other labeling in class (most recent 3) or class labeling..... ____
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☑ No
  Immediate container and carton labels ..... no
  Nomenclature review ..... na

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☑ is not on the AIP.
  Exception for review (Center Director's memo)..... na
  OC Clearance for approval..... na

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☑ Materials requested in AP letter
- Post-marketing Commitments — na
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....
- Was Press Office notified of action (for approval action only)?..... ☐ Yes ☑ No
  - Copy of Press Release or Talk Paper..... na
- Patent
  - Information [505(b)(1)] ..... ✓
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- Exclusivity Summary ..... ✓
- Debarment Statement ..... ✓
- Financial Disclosure
  - No disclosable information ..... ✓
  - Disclosable information – indicate where review is located .....
- Correspondence/Memoranda/Faxes ..... ✓
- Minutes of Meetings ..... na
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting _____
  - Date of pre-AP Safety Conference _____
- Advisory Committee Meeting ..... na
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....
- Federal Register Notices, DESI documents ..... na

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) .....
- Clinical review(s) and memoranda ..... ✓

Continued ⇨

- Safety Update review(s) ..... na

- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... ✓
  ☑ Pediatric Exclusivity requested? ☐ Denied ☑ Granted ☐ Not Applicable

- Statistical review(s) and memoranda ..... na

- Biopharmaceutical review(s) and memoranda..... ✓

- Abuse Liability review(s) ..... na
  Recommendation for scheduling ..... na

- Microbiology (efficacy) review(s) and memoranda ..... na

- DSI Audits ..... na
  ☐Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda ..... ✓
- Statistics review(s) and memoranda regarding dissolution and/or stability ..... na
- DMF review(s) ..... ✓
- Environmental Assessment review/FONSI/Categorical exemption ..... na
- Micro (validation of sterilization) review(s) and memoranda ..... na
- Facilities Inspection (include EES report)
  Date completed _____ ..... ☑ Acceptable ☐ Not Acceptable
- Methods Validation ..... ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda ..... na
- Memo from DSI regarding GLP inspection (if any) ..... |

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... na
- CAC/ECAC report 1

PATENT INFORMATION

1)	Patent No./Expiration:	U.S. Patent 4,182,763 expires May 22, 2000
	Type of Patent:	Method of use
	Patent Owner:	Bristol-Myers Squibb Company
2)	Patent No./Expiration:	U.S. Patent 5,015,646 expires May 14, 2008
	Type of Patent:	Composition of matter
	Patent Owner:	Bristol-Myers Squibb Company

CERTIFICATION OF PATENT INFORMATION

As the undersigned, I hereby make the following declaration under 21 CFR §§ 314.53(c) and 314.53(d)(2) concerning the above-listed composition and method of use patents that cover the buspirone products as described in Bristol-Myers Squibb Company's NDA for buspirone capsules.

The undersigned declares that Patent No. 4,182,763 covers the anxiolytic method of use as applied to buspirone capsules. These products are the subject of this application for which approval is being sought.

The undersigned also declares that Patent No. 5,015,646 covers the low-melting polymorphic form of buspirone hydrochloride which is incorporated into the buspirone capsules. These products are the subject of this application for which approval is being sought.

Declaration by:

Dated: 25 Aug 99

Richard P. Ryan

Richard P. Ryan, Ph.D., J.D.
Attorney for Applicants
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 18, 2000

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for BuSpar Capsules (buspirone) in 5, 7.5, 10, and 15 mg strengths

TO: File NDA 21-190
[Note: This memo should be filed with the 11-9-00 response to our 7-24-00 approvable letter.]

Buspar Tablets are approved for the treatment of generalized anxiety disorder, and are currently available in 5, 10, 15, and 30 mg strengths. This NDA provides supporting information for a capsule formulation, in 5, 7.5, 10, and 15 mg strengths.

The CMC and biopharmaceutics information were reviewed previously, and an approvable letter was issued 7-24-00. The focus of the letter was largely on asking for certain changes to the labeling, in part, new information about a very substantial food effect (about a doubling in exposure with food compared to the fasted state). In addition, we had asked for other changes previously requested but not responded to regarding an interaction with nefazodone. There was also other new drug interaction information and a geriatric use section. We had also asked BMS to provide information about the relationship of dosing to food intake in the original effectiveness trials.

Between the time of the original approvable letter (7-24-00) and now, there has been further resolution of certain of the labeling issues addressed in that letter. In particular, we agreed to language in SLR-045 that addresses the question of the buspirone/nefazodone interaction. We agreed not to contraindicate the combined use of these products, but also declined a suggested dose recommendation in the absence of sufficient safety data to justify such a recommendation.

In the 11-9-00 response, BMS has incorporated the agreed upon language from SLR-045, as well as all the other language proposed in our 7-24-00 approvable letter.

They did not respond to our question regarding information about the relationship of dosing to food intake in the original effectiveness trials.

Recommendation

Dr. Andreason has recommended that we finally approve this NDA, and I agree. However, I think the approval letter should again remind them of our question posed in the 7-24-00 letter, and ask that they respond to this following approval.

cc:
Orig NDA 21-190
HFD-120/DivFile
HFD-120/TLaughren/RKatz/PAndreason/AHomonnay

/s/

Thomas Laughren
12/18/00 11:40:41 AM
MEDICAL OFFICER

facsimile
TRANSMITTAL

[redacted]

To: Michael Eison, Ph.D., Directory, Regulatory Science
Sponsor: BMS
Fax #: (203) 677-7867
Re: NDA 18-731(10/26/00 fax concerning new CBE option for Buspar labeling supp)
Date: 10/30/00
Pages: (including cover sheet) 2

Please find attached a copy of page 10 of 23 of your October 26, 2000, fax regarding clarification for a new CBE labeling supplement option for Buspar Tablets as discussed during the October 26, 2000, teleconference between this Division and members of BMS concerning pending [redacted]

Please be reminded that due to the circumstances specified in the cover letter for [redacted] an option must be decided upon by October 31, 2000.

Thank You,

Anna Marie Homonnay, R.Ph.
Regulatory Project Manager

Center for Drug Evaluation and Research
FDA

From the desk of...

Ms. Anna M. Homonnay-Weikel, R.Ph.
Project Manager
Division of Neuropharmacological Drug Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857
301-594-5535
Fax: 301-594-2859

We have completed a cursory review of your clarification as detailed in your 10/26/00 fax for fileability as a 'Special Supplement-Changes Being Effected'. The following is the Nefazodone subsection (page 10 of 23) with the deletions that would be necessary qualify as a 'Special Supplement-Changes Being Effected' supplement from our standpoint:

> *Nefazodone:* In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg b.i.d.) with nefazodone (250 mg b.i.d.) resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in C_{max} and up to 50-fold in AUC) and statistically significant decreases (about 50%) in plasma concentrations of the buspirone metabolite 1-PP. With 5-mg b.i.d. doses of buspirone, slight increases in AUC were observed for nefazodone (23%) and its metabolites hydroxynefazodone (HO-NEF) (17%) and meta-chlorophenylpiperazine (9%). Slight increases in C_{max} were observed for nefazodone (8%) and its metabolite HO-NEF (11%).

In order to address the suggested dosing that you have proposed would require a more extensive review including the Office of Clinical Pharmacology.

APPEARS THIS WAY
ON ORIGINAL

Anna Marie,

Tom and I spoke on Friday and we felt that the deletion of any language involving "side effects" and dosing recommendations would render this a CBE instead of a prior approval submission. The following is the Nefazodone subsection with the deletions that would be necessary to bring this about.

> *Nefazodone:* In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg b.i.d.) with nefazodone (250 mg b.i.d.) resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in C_{max} and up to 50-fold in AUC) and statistically significant decreases (about 50%) in plasma concentrations of the buspirone metabolite 1-PP. With 5-mg b.i.d. doses of buspirone, slight increases in AUC were observed for nefazodone (23%) and its metabolites hydroxynefazodone (HO-NEF) (17%) and meta-chlorophenylpiperazine (9%). Slight increases in C_{max} were observed for nefazodone (8%) and its metabolite HO-NEF (11%). C

1

In order to address the suggested dosing that they propose we would have to review their argument with the Biopharm Division.

I hope that this answers your question.

Paul A.

5 Research Parkway
Wallingford, CT 06492
Tel: 203-677-6115
Fax: 203-677-7867

BRISTOL-MYERS SQUIBB

Fax

To:	Ms. Anna Marie Homonnay	**From:**	Michael S. Eison, Ph.D.
Fax:	301-594-2859	**Pages:**	24
Phone:	301-594-5535	**Date:**	October 26, 2000
Re:	Clarification of New CBE Option	**CC:**	

CONFIDENTIAL

Anna Marie,

During this morning's teleconference, Dr. Katz invited BMS to consider the option of withdrawing the September 29 CBE submission and submitting a new CBE that could contain the data (but not the dosing recommendation) regarding buspirone and nefazodone.

We would like to confirm our understanding of Dr. Katz' proposal; that is, that we could submit a CBE identical to the September 29 submission but with the deletion of the two sentences in the Nefazodone drug interaction section (page 10 of 23 in the attached mock up, dated October 25, 2000) that constituted a dosing recommendation

Thank you for your efforts to provide BMS rapid clarification of this point.

Regards,

Mike

Michael S. Eison, Ph.D.
Director, Regulatory Science
Tel.: (203) 677-6115
FAX: (203) 677-7867

23 pages redacted from this section of the approval package consisted of draft labeling

MEMORANDUM

DATE: July 22, 2000

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, 21-190

SUBJECT: Action Memo for NDA 21-190, for the introduction of BuSpar (buspirone hydrochloride) Capsules

BuSpar (buspirone hydrochloride) is an approved anxiolytic currently available only as a tablet dosage form. This NDA, submitted on 9/23/99 by Bristol-Myers Squibb Company, proposes a capsule dosage form. In support of this application, the sponsor has submitted 3 biopharmaceutics studies, dissolution data, CMC information for the new capsule, and draft labeling.

The application has been reviewed by Dr. Thomas A. Parmalee of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB; review dated 12/17/99), Dr. Lorenzo A. Rocca, division chemist (reviews dated 5/11/00 and 6/22/00), Dr. Paul J. Andreason (reviews dated 7/7/00 and including reviews dated 7/5/00 and 6/16/99, the latter 2 of which deal with previously submitted labeling supplements which are being addressed with this application). All 3 reviewers recommend that the application be considered approvable.

Currently, BuSpar tablets are available in 5 and 10 mg strengths, as well as 15 and 30 mg strengths, the latter 2 of which are designated DIVIDOSE, either of which can be broken in half or thirds, in order to provide doses of 5, 7.5, 10, 15, 20, or 30 mg. The proposed capsule strengths are 5, 7.5, 10, and 15 mg.

Study CN101-128 was done in 6 healthy subjects, who were each given a 15 mg dose of stable labeled buspirone and unlabeled buspirone at the same time. Plasma samples were obtained, and ratios of the geometric means of Cmax and AUC of the parent compound and the primary active metabolite (1-PP) were calculated for the labeled and unlabeled compounds. The 90% confidence intervals of these ratios for each species fell in the range of 0.80-1.25, demonstrating that there is no isotope effect on the kinetics of buspirone.

The definitive bioequivalence study (Study CN101-126) was done in 44 healthy subjects. This was a 2 period crossover trial in which patients got the following 2 treatments in random order: a 15 mg buspirone tablet and a 15 mg labeled buspirone solution, or a 15 mg capsule and a 15 mg labeled solution.

Ratios of Cmax and AUC for the labeled and unlabeled parent and 1-PP metabolite for each dosage form were calculated (so-called Relative Cmax and

AUC). Bioequivalence was shown by determining that the 90% confidence intervals for the ratio (test to reference) of the Relative Cmax and AUCs were entirely within 0.8-1.25 for the parent and 1-PP metabolite.

Study CN101-127 examined the effect of a high fat meal on the bioavailability of the capsule, as well as the effects of sprinkling the contents of the capsule on applesauce.

In this study, 44 healthy subjects each received the following treatments in one of four sequences:

1) 2x15 mg tablets with a high fat meal
2) 2x15 mg capsules with a high fat meal
3) 2x15 mg capsules under fasting conditions
4) 2x15 mg capsules sprinkled on applesauce and taken with a high fat meal

Important findings of this study are:

The AUC for the parent compound when given by capsule under fed conditions was about twice the AUC under fasting conditions. While there were small changes in the Cmax for both parent and 1-PP, there were no changes in the AUC of 1-PP.

There were no important differences between the capsule and tablet under the fed condition.

When the capsule contents were sprinkled on applesauce and ingested in association with a meal, there were no important differences between parent and 1-PP levels compared to when the intact capsules were given in the fed state.

When the capsule contents were sprinkled on applesauce and ingested in association with a meal, the Cmax and AUC of the parent increased by 40% and 100%, respectively, compared to when the intact capsule was ingested in the fasted state. The Cmax of 1-PP decreased by 34%, but there was no significant change in AUC.

Finally, a small (N=8) study with the buspirone tablet also revealed that the AUC and Cmax of the parent essentially doubled (84% and 116% increase, respectively) when the tablet was given in the fed as compared to the fasted state.

The sponsor has been sent a CMC deficiencies letter on 5/19/00, to which they have submitted an acceptable response (see Dr. Rocca's 6/22/00 review).

Supplement — dated — related to several drug-drug interactions involving buspirone and itraconazole, and buspirone and nefazadone.

The sponsor has also been sent several letters (the most recent being 6/1/00 to their NDA for nefazadone) informing them that we believe that the concomitant use of buspirone and nefazadone should be contraindicated. The sponsor has not incorporated this change in current labeling. Currently, labeling contains language regarding both of these interactions, with extensive language about the nefazadone interaction in the Warnings section, and language about the itraconazole interaction in the Drug Interactions sub-section, with a recommendation for a dose of buspirone of 2.5 mg BID when used with itraconazole.

COMMENTS

The sponsor has demonstrated the bioequivalence of buspirone capsules to buspirone tablets in the fasting state. In addition, they have submitted sufficient CMC information. Further, Agency reviewers have agreed with the sponsor's proposal for dissolution specifications for the capsule (see 6/12/00 memo to file describing a meeting between division chemists and the OCPB review team).

However, examination of the results of the food study reveals that exposure to the parent compound when the capsule is given with food is about twice that when the capsule is given in the fasted state. Further, if the contents of the capsule are sprinkled on applesauce, the exposure to parent compound is essentially doubled when the applesauce is taken with a meal compared to the exposure when the intact capsule is taken in the fasted state (we have no information about whether the exposure after sprinkling on applesauce and ingested with a meal is equivalent to that achieved if the contents are sprinkled on applesauce and then taken in the fasting state). In addition, a small study with the tablet alone confirms that the bioavailability of the parent when the tablet is given with food is about twice that when the tablet is given in the fasted state.

These results clearly suggest that the relationship of dosing to meals may have important effects on the resultant exposure to the relevant circulating species. For this reason, labeling should make clear this relationship, and advise prescribers about appropriate dosage adjustments, if necessary. In this regard, it may be important to examine the original studies on which approval was based, to determine whether or not attention was paid to this interaction.

In addition, I agree with the review team's recommendations about the appropriate placement of, and language for, the statements about the drug interactions (specifically, the need to contraindicate the concomitant use of buspirone and nefazadone, and the need for a lower dose of buspirone when it is given in conjunction with itraconazole, as well as the interactions with diltiazem and verapamil).

Finally, I also agree with the language proposed in Supplement 039, which refers to Geriatric experience.

For these reasons, I will issue the attached Approvable letter with draft labeling.

/s/

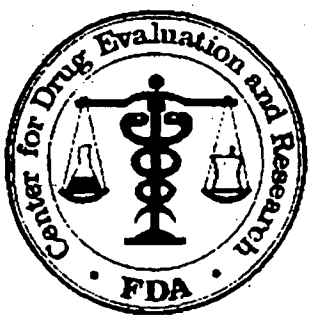
Russell Katz, M.D.

Cc:
NDA 21-190
HFD-120
HFD-120/Katz/Laughren/Andreason/Homonnay-Weikel/Seevers/Rocca
HFD-860/Parmalee/Baweja

facsimile
TRANSMITTAL

[redacted]

To: Jay Gunther
Sponsor: BMS
Fax #: (203) 677-7630
Re: NDA 21-190
Date: 5/23/00
Pages: (including cover sheet) 3



From the desk of...

Ms. Anna M. Homonnay-Weikel, R.Ph.
Project Manager
Division of Neuropharmacological Drug
Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857
301-594-5535
Fax: 301-594-2859

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 19 2000

NDA 21-190

INFORMATION REQUEST LETTER

Bristol-Myers Squibb
Attention: Jay K. Gunther, Ph. D.
Director, Worldwide Regulatory Affairs
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Gunther:

Please refer to your September 23, 1999 new drug application for BuSpar® (buspirone hydrochloride, USP) 5 mg, 7.5 mg, 10 mg, and 15 mg Capsules.

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

- **Information Pertaining to the Drug Product:**

1. The [redacted] listed in Table II.E.2.e.T01(see page 164 Vol. 1.3) is described by the trade name [redacted] however in the description of the Packaging and Labeling Procedures followed at the Mayagüez, PR facility the [redacted] is described by the trade name [redacted] (see page 162 Vol. 1.3). Please explain this discrepancy.
2. Please provide the FDA with the Bristol-Myers Squibb policy concerning [redacted] buspirone HCl [redacted] and BuSpar Capsules.
3. Please correct the following typographical error under the Materials section of [redacted] on page 254 in Vol. 1.3, change [redacted] to [redacted]
4. Please revise the Procedure section of [redacted] on page 255 in Vol. 1.3 to reflect the number of time point samples (i.e., 10 min, 20 min, 30 min, 45 min, and 60 min) that will actually be taken during dissolution testing of BuSpar Capsules.
5. Please state under the System Suitability section of [redacted] on page 256 in Vol. 1.3 the [redacted]
6. Please state under the Calculations section of [redacted] on page 256 in Vol. 1.3 the [redacted] for determining the [redacted]
7. Please revise the typical [redacted] on page 255 in Vol. 1.3 to state the [redacted] for the BuSpar Capsule 7.5 mg size formulation.
8. Please describe in greater detail (i.e., name, location, accessibility, etc.) the computer

program, which you state under the Calculations section of [redacted] on page 256 in Vol. 1.3 is the preferred means of data reduction.

9. Please label/identify the example HPLC chromatograms in [redacted] see pages 279-281 Vol. 1.3).
10. Please include an [redacted] performance test in the testing standard for [redacted] at the Mayagüez, PR facility.
11. Please provide the FDA with the testing standards used to test and release [redacted]
12. Please provide the FDA with written assurance that [redacted] component sampling and testing procedures performed at [redacted] sites are comparable to the sampling and testing procedures performed at the Bristol-Myers Squibb facilities in Mayagüez, PR and Evansville, IN.
13. Please revise the storage condition listed in the preapproval and postapproval stability protocols for BuSpar Capsules from [redacted] to 25°C±2°C/60%±5%RH, per ICH storage guidelines.
14. Please add [redacted] test to the microbial limit analysis of capsule shells or provide the FDA with scientific justification for not performing these tests.

If you have any questions, call Anna Marie Homonnay-Weikel, R. Ph. (Project Manager), at 301-594-5535.

Sincerely,

(S) 5/19/00

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-190
HFD-120/Div. Files
HFD-120/AMHomonney-Weikel
HFD-120/RSeevers
HFD-120/LRocca

Drafted by: LR/May 19, 2000
filename: C:Data\LR\nda\21190\ 21190APL.WPD

INFORMATION REQUEST (IR)

MEMORANDUM OF TELECON

NDA: 21-190

DRUG: BuSpar Capsules

SPONSOR: Bristol-Myers Squibb Company

DATE: 12/15/00

TELEPHONE NUMBER: (203) 677-6115

CONVERSATION WITH: Michael Eison, Ph.D.
Director, Regulatory Science

CONVERSATION:
Per Dr. Laughren's request I contacted BMS to confirm their agreement with the approved labeling text which will be attached to the approval letter. They agreed that the draft labeling dated 11/09/00 will be the agreed upon labeling.

/S/

Anna Marie Homonnay, R.Ph.
Regulatory Project Manager

cc:
Orig NDA 21-190
HFD-120/Div File

TELECON

/s/

Anna-Marie Homonnay
12/18/00 04:25:30 PM
CSO

Anna-Marie Homonnay
12/18/00 04:27:19 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-190

Bristol-Myers Squibb Company
Attention: Michael S. Eison, Ph.D.
Director, Regulatory Science
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Eison:

We acknowledge receipt on October 23, 2000 of your October 20, 2000 resubmission to your new drug application (NDA) for BuSpar® (buspirone hydrochloride) Capsules.

We also acknowledge receipt of your November 9, 2000, amendment.

This resubmission contains additional information concerning revisions to the labeling for BuSpar® Capsules submitted in response to our July 24, 2000 action letter.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is December 23, 2000 and the secondary user fee goal date is February 23, 2000.

If you should have any questions, please call Ms. Anna Marie Homonnay, Regulatory Project Manager, at (301) 594-5535.

Sincerely,

/S/

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 10-Nov-1999 04:07pm EST
From: Thomas Parmelee
PARMELEET
Dept: HFD-860 WOC2 5048
Tel No: 301-594-5304 FAX 301-480-3212

TO: Anna Marie Homonnay (HOMONNAYA)

CC: Raman Baweja (BAWEJA)
CC: Thomas Laughren (LAUGHREN)
CC: Thomas Parmelee (PARMELEET)

Subject: Fileability of NDA 21-190 (Buspar)

Anna Marie,

There does not appear to be any fileability issues from a PK or Biopharm perspective regarding NDA 21-190. I would like to get a desk copy of the dissolution comparison and request for biowaiver for the lower strengths of this product. I have perused through the Archival Copy (vol. 1.4) and the dissolution requirements appear to be included. My room number is 5048 and phone is 4-5304. Thanks-

-Tom Parmelee

APPEARS THIS WAY
ON ORIGINAL

APR 16 1999

IND 8,705

Bristol-Myers Squibb Company
Attention: Jay Gunther, Ph.D.
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Gunther:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for buspirone hydrochloride.

Reference is also made to your February 12, 1999, correspondence outlining your proposed development plan for a capsule dosage form for buspirone hydrochloride.

In general, we agree that the bioequivalency program that you are proposing would provide sufficient data to seek approval of a capsule dosage form, provided that the formulation remains the same as the approved tablets.

We have reviewed your proposed pharmacokinetic protocols, CN101-26, CN101-27, and CN101-128, and have the following comments:

1. Your proposed bioequivalency studies will be adequate to fulfill the requirement for *in vivo* bioequivalence studies for the new capsule dosage form.

2. Please use the FDA recommended high fat meal diet for the food effect study, Protocol CN101-127.

3. The design of Protocol CN101-127 would provide sufficient information about the effect of mixing buspirone HCl with food; however, whether such a statement will be permitted in the labeling will be dependent upon the results of the study.

If you should have any questions, please contact Ms. Anna M. Homonnay-Weikel, R.Ph., Project Manager, at (301) 594-5535.

Sincerely yours,

/S/ 4/16/99

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig IND 8705
Div File
HFD-120/Katz
HFD-120/Laughren/4.9.99Andreason/4.1.99
HFD-120/Mahmood

final: AHW/4.15.99
nda/buspar/8705cap.wpd

GENERAL CORRESPONDENCE

OCT - 6 1999

NDA 21-190

Bristol-Meyers Squibb Company
Attention: Jay K. Gunther, Ph.D.
Director, Worldwide Regulatory Affairs
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Gunther:

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

Name of Drug Product: BuSpar® (buspirone HCl) Capsules

Therapeutic Classification: Standard (S)

Date of Application: September 23, 1999

Date of Receipt: September 24, 1999

Our Reference Number: NDA 21-190

Unless we notify you within 60 days of our 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 November 24, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 24, 2000, and the secondary user fee goal date will be September 24, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, contact Anna Marie Homonnay-Weikel, R.Ph., Project Manager, at (301) 594-5535.

Sincerely,

/S/

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 21-190
HFD-120/Div. Files
HFD-120/Reviewers and Team Leaders Andreasson/Rocca
HFD-120/Homonnay
DISTRICT OFFICE

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ACKNOWLEDGEMENT (AC)

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