CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-190

Medical Review(s)

Review and Evaluation of Clinical Data
NDA #21-190

Sponsor:	Bristol-Meyers Squibb
Drug:	Buspirone (BuSpar®) Capsules
Material Submitted:	New Correspondence: Draft labeling and response to approvable action
Correspondence Date:	November 9, 2000
Date Received:	November 13, 2000

This review informs the Team Leader that the sponsor has incorporated all of the suggested language into draft labeling that was proposed in the July 24, 2000 approvable action letter. Language that was incorporated into BuSpar® tablet labeling, via NDA 18-731 SLR-045, was also incorporated into this version of the sponsor's draft labeling.

Background
BuSpar® (buspirone hydrochloride) is approved for the treatment of anxiety most closely resembling DSM-IV generalized anxiety disorder. The sponsor submitted NDA 21-190 for a new capsule formulation that is bioequivalent to the tablet formulation (NDA 18-731).

This revision incorporates all of the proposed draft labeling changes that were communicated in the July 24, 2000 approvable action letter, and it incorporates labeling modifications provided by the CBE labeling supplement SLR-045 to NDA 18-731. There are only minor stylistic differences between the proposed labeling in this submission and the Division's proposed labeling from July 24, 2000.

Conclusions and Recommendations
The draft labeling provided in this submission is in agreement with the Division's proposed draft labeling that was communicated in the July 24, 2000 approvable action letter. Changes incorporated in this draft labeling also accurately reflect changes incorporated in BuSpar® tablet formulation labeling from SLR-045 (NDA 18-731).

I recommend that the Division approve the sponsor's currently proposed draft labeling as it is written.

/S/

Paul J. Andreason, M.D.

cc: NDA# 21-190
HFD-120
HFD-120/
P Andreason
AM Homonnay
T Laughren

/s/

Paul Andreason
12/13/00 07:37:13 AM
MEDICAL OFFICER

Thomas Laughren
12/13/00 11:18:29 AM
MEDICAL OFFICER
I concur with the reviewer's recommendations.--TPL

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Review and Evaluation of Clinical Data
NDA #21-190

Sponsor:	Bristol-Meyers Squibb
Drug:	Buspirone (BuSpar®) Capsules
Material Submitted:	General Correspondence: Draft labeling in electronic format.
Correspondence Date:	May 23, 2000
Date Received:	May 24, 2000

Background

BuSpar® (buspirone hydrochloride) is approved for the treatment of anxiety most closely resembling DSM-IV generalized anxiety disorder. It is an agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative anxiolytic drugs. The sponsor submitted NDA 21-190 for a new capsule formulation that is bioequivalent to the tablet formulation.

This revision is based on the version of labeling submitted on 5/23/2000 and also incorporates labeling modifications provided by the labeling supplements SLR-037 and SLR-039.

Conclusions and Recommendations

The **CLINICAL PHARMACOLOGY** section was changed to detail the pharmacokinetic studies and leave intact the previous study description of food effects on the tablet.

I recommend the following in the **CONTRAINDICATIONS** section. The sponsor proposed a maximum dose of 2.5 mg BID of Buspar when it is used in combination with nefazodone in SLR-037. However, in the case of buspirone given in combination with nefazodone, based on extrapolation of known pharmacokinetic data, this dose would produce Cmax and AUC values that would fall above the AUC and Cmax for the highest recommended dose for Buspar. Given the available tablet strengths of Buspar, it would not be possible to reasonably titrate patients within the currently recommended exposure range for this product. I therefore recommend, as previously communicated, that the concomitant use of Buspar and nefazodone be contraindicated.

I recommend the following change in the *Drug Interactions* section. Using the linear extrapolation to judge the appropriateness of the sponsor's previous labeling suggestions for itraconazole, one finds that the seemingly conservative suggestion of 2.5 mg BID produces an AUC of 13.7ng.hr/ml. A single daily dose of 2.5 mg would produce an AUC of 6.9 ng.hr/ml and this would be less than the upper limit of 8.7 ng.hr/ml with 60-mg/day. Therefore we recommend a single daily dose of 2.5-mg/day with itraconazole

I also recommend that the description of the study describing the interactions of buspirone and verapamil and diltiazem be added to the *Drug Interactions* section.
The sponsor's draft labeling suggests dosing in the *Potential Interaction with Drugs That Inhibit Cytochrome P450 3A4 (CYP3A4)* subsection. I do not agree with suggesting a general dosing regimen in the absence of supporting pharmacokinetic data. Therefore the section is changed to reflect a general cautionary statement based on known data.

On June 27, 2000 the sponsor proposed draft-labeling changes to the *Geriatric Use* section that are acceptable. Those changes are incorporated in this version of draft labeling.

I recommend that the Division make an approvable action on this NDA pending the above modifications to labeling.

S 7/7/00

Paul J. Andreason, M.D.

cc: NDA# 18-731
HFD-120
HFD-120/
P Andreason
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7-9-00

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