CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-190

Chemistry Review(s)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

JUN 27 2000

NDA 21-190 **CHEM REVIEW: #2** **REVIEW DATE: 6/22/00**

SUBMISSION TYPE	DOC. DATE	CDER DATE	ASSIGNED DATE	ACTION
ORIGINAL	09/23/99	09/24/99	10/01/99	Inf. Request Letter 05/19/00
Amendment N(BC)	06/08/00	06/12/00	06/20/00	Reviewed 06/22/00

NAME AND ADDRESS OF APPLICANT

Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

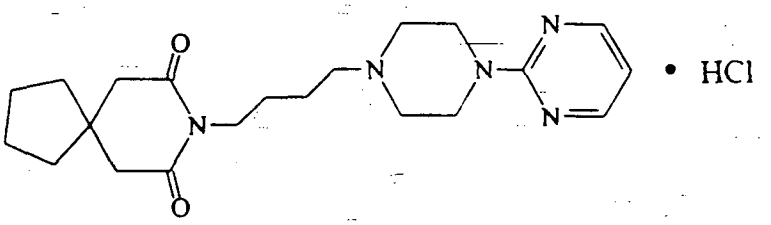
DRUG PRODUCT NAME

Proprietary:	BuSpar®
Non proprietary/USAN:	Buspirone HCl, USP
Code Name/Number:	MJ-9022
Chem. Type/Ther. Class:	

PHARMACOLOGICAL CATEGORY/INDICATION:	Anti-Anxiety Agent
DOSAGE FORM:	Capsule
STRENGTHS:	5 mg, 7.5 mg, 10 mg, 15 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	_X_Rx ___OTC
SPECIAL PRODUCTS:	____Yes _X_No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

CA Name: N-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-1,1-cyclopentanediacetamide monohydrochloride
USAN Name: Buspirone Hydrochloride
Chemical Formula: $C_{21}H_{31}N_5O_2 \cdot HCl$
Molecular Weight: 421.96 (HCl), 385.50 (free base)
CAS Registry Number: 59729-32-7 [buspirone HCl], 36505-84-7 [buspirone]
Laboratory Code:
Synonyms: BuSpar®
Chemical Structure:



SUPPORTING DOCUMENTS:

TYPE/NUMBER	SUBJECT	HOLDER/SPONSOR	STATUS	REVIEW DATE	LETTER DATE
IND 8,705	Buspirone HCl	Bristol-Myers Squibb	CMC reviews up to date	Not Applicable	Not Applicable
IND 58,132	Buspirone HCl Capsules	Bristol-Myers Squibb	CMC reviews up to date	Not Applicable	Not Applicable
NDA 18-731	BuSpar® (buspirone HCl, USP) Tablets	Bristol-Myers Squibb	CMC reviews up to date	Not Applicable	Not Applicable
DMF (Type III)			Sufficient data provided by NDA sponsor	Not Applicable	Not Applicable
DMF (Type III)			Sufficient data provided by NDA sponsor	Not Applicable	Not Applicable
DMF (Type III)			Sufficient data provided by NDA sponsor	Not Applicable	Not Applicable
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DMF (Type III)			Adequate	Reviewed by James D. Vidra on 9/22/99	Not Applicable
DMF (Type III)			Adequate	Reviewed by Donald N. Klein on 7/27/99; Telecon Lorenzo Rocca — on 4/27/00	Not Applicable

SUPPORTING DOCUMENTS: Continued

TYPE/NUMBER	SUBJECT	HOLDER/SPONSOR	STATUS	REVIEW DATE	LETTER DATE
DMF — (Type III)	—	—	Adequate	Reviewed by Raymond P. Frankewich on 2/25/99	Not Applicable
DMF — (Type III)	—	—	Adequate	Reviewed by Shing H. Liu on 3/6/00 Reviewed by Xavier Ysern on 9/16/98	Not Applicable
DMF — (Type IV)	—	—	Adequate	Reviewed by Susan Zuk on 9/22/99	Not Applicable
DMF — (Type IV)	—	—	Adequate	Reviewed by Sung K. Kim, Ph.D. on 1/07/00	Not Applicable

RELATED DOCUMENTS: N/A

CONSULTS: N/A

OTHER REQUESTS:

Request	Status	Status of Request
Establishment Evaluation	8 sites found acceptable	Submitted on 11/5/99: CFN 2627673: Acceptable on 3/27/00 (district recommendation) CFN 2623241: Acceptable on 11/8/99 (based on profile) CFN 1819504: Acceptable on 11/5/99 (based on profile) CFN 1421377: Acceptable on 11/5/99 (based on profile) CFN 1317461: Acceptable on 12/7/99 (district recommendation) CFN 2518332: Acceptable on 2/7/00 (district recommendation) CFN 1118920: Acceptable on 4/12/00 (district recommendation) Submitted on 11/23/99: CFN 9613225: Acceptable on 12/1/99 (district recommendation)
Methods Validation	Submitted 6/20/00	The methods validation package was sent to the Philadelphia District Laboratory, HFR-MA160 for evaluation.

Related Reviews:

Clinical Pharmacology/Biopharmaceutics Review #1; Thomas A. Parmelee, Pharm. D. (HFD-860), Review #1: 12/17/99; Supervisory concurrence, R. Baweja, Ph. D., 12/17/99 Pharmacology/Biopharmaceutics Memorandum; Hong Zhao, Ph.D. (HFD-860), Memorandum: 6/12/00; Supervisory concurrence, R. Baweja, Ph.D., 6/12/00	Biopharm Recommendation: NDA 21-190 meets the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) requirements and is approvable provided the product labeling is amended as recommended. • The request for waiver for bioequivalence testing on the 5, 7.5, and 10 mg strength capsules is granted because bioequivalency has been shown between the capsule and tablet at the highest strength of 15 mg, and based on the proportional similarity of qualitative and quantitative composition between capsule strengths. In addition, similar dissolution profiles have been shown for each capsule strength. • The final product-labeling insert for BuSpar Capsules should resemble the currently approved labeling insert for BuSpar Tablets with recommended additions under the Sections of the label insert entitled Clinical Pharmacology and Drug Interaction.

REMARKS/COMMENTS:

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) in their review of NDA 21-190 (see OCPB Review #1, December 17, 1999) recommended the following dissolution methodology and specifications for BuSpar Capsules:

- Method- USP Apparatus 2 (paddle), 50 rpm, 500 mL of 0.01N HCl at 37°C.
- Spec- Q not less than ~ % in _ minutes.

On June 6, 2000 Lorenzo Rocca, Ph.D. (HFD-120) and his supervisor Robert H. Seevers. Ph.D. (Group Leader HFD-120) meet with Ray Baweja, Ph.D. the Biopharm team leader and Hong Zhao, Ph.D. the current Biopharm reviewer assigned to NDA 21-190, in order to discuss Biopharm's recommended dissolution specification for BuSpar® (buspirone HCl) Caplsules. Based on the drug product stability presented in NDA 21-190 it was agreed that a dissolution specification of Q not less than ~ % in _ minutes was not appropriate. Chemistry and Biopharm agreed a dissolution specification of Q not less than 80% in 30 minutes is appropriate for BuSpar Capsules. The agreed upon dissolution specification for BuSpar Capsules is the same as the dissolution specification proposed by Bristol-Myers Squibb in NDA 21-190. Dr. Hong Zhao prepared a memorandum (see OCPB memorandum, June 12. 2000) describing the Chemistry and Biopharm decision concerning the dissolution specification for BuSpar Capsules.

CONCLUSIONS & RECOMMENDATIONS: Concerning the chemistry, manufacturing, and controls (CMC), NDA 21-190 is recommended for approval. The methods validation package for NDA 21-190 has been submitted to the appropriate FDA Pre-Approval Laboratory.

/S/ 6/22/00

Lorenzo A. Rocca, Ph.D., Review Chemist

/S/ 6/27/00

Robert H. Seevers, Ph.D., Chemistry Team Leader

cc:
NDA 21-190
HFD-120/Division File
HFD-120/AMHomonnay-Weikel
HFD-120/LRocca
HFD-120/RSeevers
HFD-860/RBaweja
HFD-860/HZhao
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MEMORANDUM

To: Division File NDA 21-190

From: Bob Seevers /S/ 5/19/00

Date: May 19, 2000

Re: Transmittal of Lorenzo Rocca's Chemistry Review #1 for NDA 21-190

This memorandum is to transmit Lorenzo Rocca's Chemistry Review # 1 for NDA 21-190, BuSpar® (buspirone HCl) capsules, to the Division File. It should be noted that there is a difference in the recommended dissolution specification between the OCPB review by Thomas Parmalee and that given in the chemistry review by Lorenzo Rocca. The OCPB recommendation is Q of not less than —— —— Dr. Rocca's recommendation is for of not less than 80% in 30 minutes, which the same as what the firm proposes and the same as the specification for the corresponding tablet dosage form (NDA 18-731).

I concur with Dr. Rocca's recommendation based on the stability data presented in the application which indicate that the capsule drug product would fail the —minute specification by the end of its shelf life. I have discussed this with Dr. Ray Baweja, the Biopharm team leader, and we have agreed that Dr. Rocca and Dr. Hong Zhao, the present Biopharm reviewer assigned to this application should discuss this and resolve this difference prior to the action date.

cc
NDA 21-190
HFD-120/LRocca
HFD-120/RSeevers
HFD-120/RBaweja
HFD-120/HZhao
HFD-120/AHomonnay

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

MAY 19 2000

NDA 21-190 **CHEM REVIEW: #1** **REVIEW DATE: 5/11/00**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	ACTION
ORIGINAL	09/23/99	09/24/99	10/1/99	

NAME AND ADDRESS OF APPLICANT

Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

DRUG PRODUCT NAME

Proprietary:	BuSpar®
Non proprietary/USAN:	Buspirone HCl, USP
Code Name/Number:	MJ-9022
Chem. Type/Ther. Class:	

PHARMACOLOGICAL CATEGORY/INDICATION:	Anti-Anxiety Agent
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ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	_X_Rx ___OTC
SPECIAL PRODUCTS:	____Yes _X_No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

CA Name: N-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-1,1-cyclopentanediacetamide monohydrochloride
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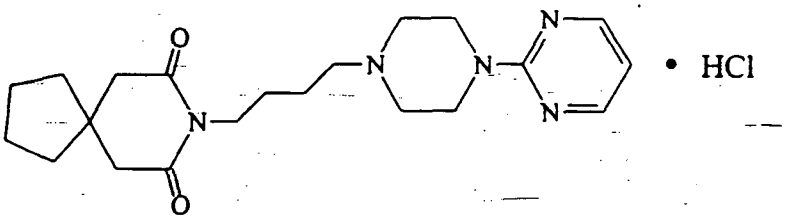
Laboratory Code:
Synonyms: BuSpar®
Chemical Structure:



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RELATED DOCUMENTS: N/A

CONSULTS: N/A

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Methods Validation	Pending	Will be submitted after all the CMC deficiencies have been addressed.

Related Reviews:

Clinical Pharmacology/Biopharmaceutics Review; Thomas A. Parmelee, Pharm. D. (HFD-860), Final Review: 12/17/99; Supervisory concurrence, R. Baweja, Ph. D., 12/17/99	Biopharm Recommendation: NDA 21-190 meets the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) requirements and is approvable provided the dissolution specifications and product labeling are amended as recommended. • The proposed dissolution specification of Q not less than 80% in 30 minutes is not acceptable to OCPB based on the dissolution profiles submitted to OCPB. OCPB recommends Q not less than —— Methodology is unchanged • The request for waiver for bioequivalence testing on the 5, 7.5, and 10 mg strength capsules is granted because bioequivalency has been shown between the capsule and tablet at the highest strength of 15 mg. and based on the proportional similarity of qualitative and quantitative composition between capsule strengths. In addition, similar dissolution profiles have been shown for each capsule strength. • The final product-labeling insert for BuSpar Capsules should resemble the currently approved labeling insert for BuSpar Tablets with recommended additions under the Sections of the label insert entitled Clinical Pharmacology and Drug Interaction.

REMARKS/COMMENTS:

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) in their review of NDA 21-190 (see OCPB review, December 17, 1999) recommends the following dissolution methodology and specifications for BuSpar Capsules:

- Method- USP Apparatus 2 (paddle), 50 rpm, 500 mL of 0.01N HCl at 37°C.
- Spec- Q not less than ——

The OCPB recommended dissolution methodology is the same as proposed by Bristol-Myers Squibb. The recommended dissolution specification represents a change of the sponsors proposed dissolution specification from a Q not less than 80% in 30 minutes to a Q not less than —— After examining the dissolution profile presented by the sponsor in their validation of dissolution HPLC method —— as well as the dissolution profiles of BuSpar Capsules at the 3-month time point in the sponsor's preapproval stability study (Stability Protocol 321), this reviewer does not favor, at this time, tightening the dissolution specification for BuSpar Capsules. The dissolution data presented at the 3 month preapproval stability time point, in order to meet a dissolution specification

of Q not less than — would have required — dissolution testing of BuSpar Capsules 5 mg, 7.5 mg, 10 mg, and 15 mg after storage 3 month at 25°C/60%RH in — bottles, and unit-dose blisters. — The sponsor is claiming a three year expiry period for drug product packaged in — bottles or blisters, when protected from temperatures greater than 86°F (30°C). In the opinion of this reviewer, a tighter dissolution specification for BuSpar Capsules is not justified at this time. It should be noted that the dissolution specification for BuSpar Tablets is not less than a Q of 80% in 30 minutes, and BuSpar Tablets are bioequivalent to BuSpar Capsules.

CONCLUSIONS & RECOMMENDATIONS: Concerning the chemistry, manufacturing, and controls (CMC), NDA 21-190 is approvable. The Applicant must address the CMC deficiencies before the NDA can be approved for CMC. See draft deficiency letter.

The sponsor proposed three-year expiry period for BuSpar® (buspirone HCl, USP) is supported by the following stability studies:

- Historical stability studies performed on 5 mg and 10 mg buspirone HCl capsules — packaged in — bottles and in — unit dose blisters. Drug product was stored at room temperature (30°C) for up to four years, 40°C testing for one year, and 38°C/80%RH and 30°C/70%RH testing at six months, with additional testing at 50°C, -18°C, freeze-thaw cycle, and room light and intense light conditions.
- Preapproval stability studies — on each strength of BuSpar Capsules packaged in — bottles and — unit-dose blisters are ongoing. Stability samples are stored at 25°C/60%RH for long-term (36 months) stability and 40°C/75%RH for short term (6 months) accelerated stability (i.e., ICH conditions). In addition, testing at 30°C/60%RH will be conducted through two years. The three-month stability report — for the ongoing preapproval stability study of BuSpar Capsules is included in NDA 21-190.

/S/ 5/11/00

Lorenzo A. Rocca, Ph.D., Review Chemist

/S/ 5/19/00

Robert H. Seevers, Ph.D., Chemistry Team Leader

cc:
Orig. NDA 21-190
HFD-120/Division File
HFD-120/AMHomonnay-Weikel
HFD-120/LRocca
HFD-120/RSeevers
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