CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-152/S-009/S-010

ADMINISTRATIVE DOCUMENTS

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION **APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE** *(Title 21, Code of Federal Regulations, 314)*	*Form Approved: OMB No. 0910-0001* *Expiration Date: December 31, 1992* *See OMB Statement on Page 3.* FOR FDA USE ONLY DATE RECEIVED / DATE FILED DIVISION ASSIGNED / NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT Bristol-Myers Squibb Pharmaceutical Research Institute	DATE OF SUBMISSION April 10, 1997
ADDRESS *(Number, Street, City, State and Zip Code)* 5 Research Parkway - P.O. Box 5100 Wallingford, CT 06492-7660	TELEPHONE NO. *(Include Area Code)* (203) 284-6259 NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) 20-152

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)* Nefazodone hydrochloride (USAN) Nefazodone (INN)	PROPRIETARY NAME *(If any)* SERZONE®
CODE NAME *(If any)* BMY-13754-1. MJ-13754	CHEMICAL NAME 2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]-propyl]5-ethyl-2,4-dihydro-4-(2-phenoxy-ethyl)-3H-1,2,4-triazol-3-one hydrochloride

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Tablets	Oral	50, 100, 150, 200, 250 and 300 mg.

PROPOSED INDICATIONS FOR USE

Treatment of depression

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)* AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☒ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70 (b)(2)(iv))*

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d)(1))
	4. a. Samples (21 CFR 314.50 (e)(1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e)(2)(i))
	c. Labeling (21 CFR 314.50 (e)(2)(ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling *(12 copies)*
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d)(2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d)(3))
	7. Microbiology section (21 CFR 314.50 (d)(4))
	8. Clinical data section (21 CFR 314.50 (d)(5))
	9. Safety update report (21 CFR 314.50 (d)(5)(vi)(b))
	10. Statistical section (21 CFR 314.50 (d)(6))
	11. Case report tabulations (21 CFR 314.50 (f)(1))
	12. Case report forms (21 CFR 314.50 (f)(1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
X	15. OTHER *(Specify)* Supplemental Application: Labeling

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Jay K. Gunther, Ph.D., Director Worldwide Regulatory Affairs		4/10/97

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
Bristol-Myers Squibb Pharmaceutical Research Institute 5 Research Parkway - P.O. Box 5100 Wallingford, CT 06492-7660	(203) 284-6259

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

FORM FDA 356h (6/92)

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Bristol-Myers Squibb
Pharmaceutical Research Institute

NDA SUPPL AMEND

SLR-009 (BL)

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

NDA No. 20-152
SERZONE® (Nefazodone HCl) Tablets

Submission No. 127: Supplemental Application: Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 11 1997
HFD-12

April 10, 1997.

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room, HFD-120
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Leber:

Reference is made to our approved New Drug Application for SERZONE® (Nefazodone Hydrochloride) Tablets (NDA No. 20-152) and to the Administration's letter dated May 23, 1996, requesting Bristol-Myers Squibb to revise the labeling for SERZONE to contraindicate the coadministration of nefazodone and triazolam. Further reference is made to our submission of June 28, 1996, concerning this request and to the Administration's response dated September 11, 1996, which repeated the request to revise the SERZONE labeling. Finally, reference is made to our Supplemental Application to NDA 20-152 dated November 20, 1996 (Supplement S-009) and to the telephone conversation between yourself and the undersigned on February 13, 1997.

Supplement S-009 proposed revised labeling for SERZONE that was intended to address the Administration's concerns about the concomitant use of nefazodone and triazolam. In this revision the **Triazolam** subsection of the **WARNINGS** section had been modified to indicate that, because commercially available dosage forms of triazolam do not permit sufficient reductions in dosage, the coadministration of triazolam and nefazodone should be avoided for most patients. In the telephone conversation referred to above, you indicated that this warning was not sufficient. During the discussion, it was suggested that a similar statement be added to the **CONTRAINDICATIONS** section of the labeling and this proposal has been accepted by Bristol-Myers Squibb. The purpose of this submission is to formally amend Supplement S-009 by submitting labeling that has been revised in accordance with that proposal. Please see Attachment A for the draft labeling. For the convenience of the reviewers, with the Archival copy of this submission, we are providing an electronic (WordPerfect 6.1) version of the draft labeling. A printed copy of the electronic version is provided in Attachment B. Please note that in the WP 6.1 version of the label, the additions to the current labeling have been "red-lined" while the deletions have been "struck-out".

Bristol-Myers Squibb acknowledges that the Administration has the responsibility to ensure that, as new information becomes available, a drug's labeling is updated to provide adequate directions for its safe and effective use. We are most willing to cooperate with the Agency in such matters, but we would like to express our concern that it appears that such labeling changes are not a universal practice. For example, the labeling for SERZONE has contraindicated its use with terfenadine and astemizole since the nefazodone NDA was approved in December 1994. Another example is the contraindication about the use of nefazodone with cisapride that was added at the Administration's request to the SERZONE labeling in October 1995. These contraindications are warranted because the combined use of these drugs with nefazodone could lead to elevated plasma levels that have been associated with QT prolongation and serious cardiovascular adverse events. However, to date there have been no changes in the labeling for either terfenadine, astemizole or cisapride to contraindicate their use with nefazodone. This failure to revise the labeling is especially perplexing since it is the elevated levels of these drugs that lead to QT prolongation. We assume the Agency has approached the manufacturers of these drugs and urged them to revise their labels, but we have no knowledge of such an action. If it is important that SERZONE and HALCION labeling be consistent with regards to the combined use of the two drugs, we would certainly expect the Administration to continue to use all efforts at its means to ensure that the labeling for terfenadine, astemizole and cisapride be consistent with nefazodone's.

We trust the Administration will find the draft labeling satisfactory and we look forward to prompt approval of Supplement S-009. If there are any questions or comments regarding this submission, please contact the undersigned at (203)-284-6259.

Very truly yours,

BRISTOL-MYERS SQUIBB COMPANY

Jay K. Gunther. Ph.D.
Director
Worldwide Regulatory Affairs

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Attachments

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Bristol-Myers Squibb
Pharmaceutical Research Institute

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

NDA SUPPL AMEND

SLR-010 (AL)

NDA No. 20-152
SERZONE® (Nefazodone HCl) Tablets

Submission No. 128:
Supplemental Application:
Labeling

April 10, 1997

CENTER FOR DRUG
REC'D
APR 11 1997
HFD-120
EVALUATION AND RESEARCH

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room, HFD-120
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Leber:

Reference is made to our approved New Drug Application for SERZONE® (Nefazodone Hydrochloride) Tablets (NDA No. 20-152) and to our supplemental application dated November 21, 1996, to that NDA (S-010). Further reference is made to the Administration's letter dated January 31, 1997, indicating that supplement S-010 had been reviewed and found unacceptable.

Supplement S-010 proposed modifications to the labeling for SERZONE that [redacted] and add a Postintroduction Clinical Experience subsection to the **ADVERSE REACTIONS** section. The application also proposed listing the terms "priapism" and "convulsions (including grand mal seizures)" in the new Postintroduction Clinical Experiences subsection. This proposal was made in response to the Administration's request of September 12, 1996, that we reword the Priapism subsection in the current labeling. In the letter of January 31, 1997, referred to above, the Administration indicated that S-010 is not acceptable because in its opinion these two adverse experiences require a greater prominence than a mention in the Postintroduction Clinical Experience subsection.

The purpose of this submission is to formally amend Supplement S-010 by proposing revised labeling for SERZONE that addresses the concerns expressed in the letter of January 31, 1997. We have revised both the Priapism and the Seizures subsections of the **PRECAUTIONS** section to indicate that we have received post-marketing reports of these adverse experiences. We have also continued to list these adverse experiences in the Postintroduction Clinical Experience subsection. Copies of

the reports of these adverse experiences that have been received by Bristol-Myers Squibb were included in our submission dated November 21, 1996. Please see Attachment A for the draft labeling. For the convenience of the reviewers, we are providing an electronic (WordPerfect 6.1) version of the draft labeling with the Archival copy of this submission. A printed copy of the electronic version is provided in Attachment B. Please note that in the WP 6.1 version of the label, the additions to the current labeling have been "red-lined" while the deletions have been "struck-out".

We believe the revised labeling addresses the concerns expressed by the Administration and we trust we may look forward to a prompt review and approval of this supplement. If there are any questions or comments concerning this application, please contact the undersigned at (203)-284-6259.

Very truly yours,

BRISTOL-MYERS SQUIBB COMPANY

Jay K. Gunther. Ph.D.
Director
Worldwide Regulatory Affairs

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Attachments