CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-152/ S-031

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-152/S-031

Bristol-Myers Squibb Company
Attention: Michael S. Eison, Ph.D.
Global Regulatory Liaison
Five Research Parkway
Wallingford, CT 06492

Dear Dr. Eison:

Please refer to your supplemental new drug application dated January 29, 2002, and received on January 31, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Serzone (nefazodone hydrochloride) 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg Tablets.

We additionally acknowledge receipt of your amendment dated February 6, 2002.

This "Prior Approval" supplemental new drug application provides for a response to an Agency letter dated December 13, 2001, related to twenty-three medication error reports involving confusion between Serzone and Seroquel (quetiapine fumarate) tablets.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues.

Your response proposes to use the following components in your risk management program:

1. Drug Product – Packaging Changes
   Emphasize the unique part of a drug's name (e.g., serZONE).

2. Communications to Pharmacists
   Disseminate a "Dear Pharmacist Letter" describing the details of the name.

Although we believe that the above components in your risk management program will assist in reducing this medication error, we additionally believe that BMS should incorporate the following additional strategies into the Serzone risk management program:

Sponsor Generated Actions

1. Press release to announce education program (with Division pre-approval).

2. Sales force training to convey warnings about prescribing and dispensing errors to physicians and pharmacists.
3. Offer assistance of a 1-800 number and website.
4. Work with company that programs pharmacy print-outs that are stapled to dispensed prescriptions to add a warning regarding name confusion.

Drug Product - Packaging Changes

- Distinguish the bottle in some way, such as a sticker on the bottle cap or a different colored cap.

Activities for Pharmacists

1. Communications to Pharmacists
   - Periodic reminder dispensing error alerts.
   - Advertisements in key pharmacy journals.
   - Distribution of educational item to hospital and retail pharmacies by sales staff.
   - Convention panel for display at important pharmacy meetings.
   - Live telephone conferences to alert pharmacists to differentiate between the drugs being confused.
   - Editorials in pharmacy newsletters.
2. Use of shelf tags to alert dispensing pharmacist of potential name confusion (send with "Dear Pharmacist Letter" to ensure distribution).
3. Incorporation of computer screen alert.
4. Encouragement of good dispensing practices using reminder card.

Activities for Physicians

1. Communications to Physicians
   - Disseminate a "Healthcare Provider Letter" describing the details of the name confusion. This letter should be placed in an envelope with "Important Drug Warning" stamped on the envelope in accordance with 21 CFR 200.5. We request that you provide the Division with a draft version of the letter prior to dissemination.
   - Encourage good prescribing practices during standard visits by sales representatives.
   - Encourage physicians to promote good prescribing practices among members of office staff phoning in prescriptions to pharmacies.
   - Upgrade all physician materials to include a message warning of name confusion.
   - Advertisements in key medical journals.
   - Convention panel for display at pertinent medical meetings.
   - Work through appropriate professional societies to disseminate information regarding name confusion.
2. Consider pre-printed prescription pads.

Activities for Patients

1. Communications to Patients/Patients' Families
   - Work through patient advocacy groups to disseminate information regarding name confusion.

2. Upgrade all "direct-to-consumer" advertisements to include a message warning of name confusion.
3. Distribute informational item displaying appearance of the intended drug product (e.g., wallet card).
4. Provide patient brochures with large, clear pictures of the medication.
5. Encourage patients to talk to pharmacist if received medication does not look like prescribed medication.

Evaluative and Follow-up Measures

1. Report newly identified prescribing and dispensing errors in an expedited manner (e.g., monthly to start)
2. If packaging changes were instituted to ease product identification, involve pharmacists in the evaluation of the usefulness of these changes at some predetermined time period following the institution of the change.
3. Conduct survey of prescribers and dispensers to assess efficacy of educational/awareness program.

Although we are requesting that you augment your Serzone risk management program in order to satisfactorily address this public health concern, we believe that you should implement the changes proposed in your January 30, 2002 submission, i.e., "Dear Pharmacist Letter" and container changes, immediately.

Additionally, we encourage you to work closely with Astra Zeneca, the sponsor of Seroquel, in order to efficiently implement these additional risk management strategies.

We additionally request that you respond to this letter within 60 days of the signature date.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
4/26/02 08:10:25 AM

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Public Health Service

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We acknowledge receipt of your submission dated June 21, 2002. Your submission of June 21, 2002 constituted a complete response to our April 26, 2002 action letter.

This "Prior Approval" supplemental new drug application provides for a response to Agency letters dated December 13, 2001, and April 26, 2002, related to twenty-three medication error reports involving confusion between Serzone and Seroquel (quetiapine fumarate) tablets and your efforts to disseminate the message regarding name confusion between Serzone and Seroquel.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments and questions as described below:

1. The statement you intend to add to pharmacy print-outs (point #4 under "Sponsor-Generated Actions") is not adequate because reading the drug name on the label does not ensure that the pills in the bottle match the name on the bottle label. It would be preferable if the statement said something like "Before taking this medication, check the pills in the bottle to make sure that they match the picture of the medication on the patient brochure."

2. Please update us on the status of the incorporation of the message about Serzone-Seroquel name confusion into a pharmacy computer screen alert.

3. We note that you have disseminated the "Dear Pharmacist" letter. We request that you send the letter to physicians/health care providers as well, as some of the medication errors stemmed from physician (or physician office) actions. We have attached a version of the "Dear Pharmacist" letter edited for health care providers.

4. Please clarify the use of the patient brochure. Is your intent/expectation that this brochure be distributed to all patients who are initiated on Seroquel? How do these brochures get to the patients (e.g., from the physician or the pharmacist)?

5. Surveillance for new instances of prescribing and dispensing errors should be conducted on an ongoing basis, with updates to us provided on a monthly basis.

6. The USP Medication Errors Reporting Program is not designed to address the effectiveness of educational programs aimed at raising awareness of specific name confusion pairs. We request that you conduct your own survey to determine the effect of your educational campaign on the awareness of the name confusion issue with Serzone and Seroquel.

We additionally request that you respond to this letter within 60 days of the signature date.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

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Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
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Attachment

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X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Russell Katz
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