

## REVIEW AND EVALUATION OF CLINICAL DATA

**NDA: 20-152**

**SUPPLEMENT:** (b) (4)

**SPONSOR: BRISTOL-MYERS SQUIBB**

**DRUG: NEFAZODONE HYDROCHLORIDE (SERZONE)**

**MATERIAL SUBMITTED: Pediatric Exclusivity Supplement**

**DATE SUBMITTED: 4-16-02**

**PDUFA DUE DATE: 10-17-02**

**REVIEWER: Andrew D. Mosholder, M.D., M.P.H.**

### Executive Summary

#### I. Recommendations

I recommend (b) (4) for this supplement.

#### II. Summary of Clinical Findings

A. Brief Overview of Clinical Program: The following table describes the three clinical trials in this submission.

Study	Description
CN104136	Open label, 8 week pharmacokinetic study; nefazodone 50-300 mg/day (children) and 100-600 mg/day (adolescents); n=28; included long term open label followup treatment $\geq$ 18 weeks.
CN104141	Randomized, double blind, placebo controlled, multicenter, 8 week trial. Nefazodone 100-600 mg/day versus placebo; n=201 depressed adolescents. Double blind extension treatment of up to 26 weeks.
CN104187	Randomized, double blind, placebo controlled, multicenter, 8 week trial. Nefazodone 100-300 mg/day, nefazodone 200-600 mg/day and placebo; n= 278 children and adolescents with depression. Open label follow up treatment of up to 26 weeks.

This supplement includes safety information on a total of 371 pediatric patients exposed to nefazodone (133 children and 238 adolescents). The total exposure to nefazodone in these trials was 115 person-years. A total of 97 subjects received nefazodone for over 180 days.

#### B. Efficacy

The results for the two efficacy trials are shown below. Please refer to the table above for information on the study design.

Study 187:

(b) (4)

(b) (4)

Study 141:

(b) (4)

(b) (4)

This study provides some evidence that nefazodone is active in the treatment of adolescent major depressive disorder. However, the difference between placebo and nefazodone was only marginally statistically significant (b) (4). Therefore, although there is some evidence of a drug effect, this study does not meet the usual statistical criteria for a positive efficacy trial.

- C. Safety: Based upon these trials, the safety profile for nefazodone in the pediatric population does not appear to be significantly different from that in adults. Two nefazodone-treated subjects in these studies developed clinically significant rashes, but causality is difficult to assess.
- D. Dosing: No dosing recommendations can be made based upon these data, since efficacy in the pediatric population was not established.
- E. Special Populations: This supplement is limited to data in the pediatric population.

## **Clinical Review**

### I. Introduction and Background

#### A. Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

The sponsor is not seeking an indication for pediatric major depressive disorder. Bristol-Myers Squibb's proposed labeling is as follows:



#### A. State of Armamentarium for Indication

Serzone is indicated for the treatment of adult major depressive disorder. No drug products are currently indicated for the treatment of pediatric major depressive disorder, although Prozac has received an approvable action for this claim.

#### C. Important Milestones in Product Development

Serzone was approved for marketing in the U.S. in December 1994. As a Phase IV commitment, FDA requested the sponsor to study the safety, efficacy and pharmacokinetics of nefazodone in children and adolescents. Pursuant to this Phase IV commitment, Bristol-Myers Squibb (BMS) conducted study CN104-136, the pharmacokinetic study in this supplement, and submitted the results in January 1998. The agency issued a Written Request (WR) for Serzone on 4-28-99; the WR called for two randomized, double blind, placebo controlled trials, a pharmacokinetic study, and longer term safety data. The WR was amended on 4-9-00, as proposed in a submission from BMS 11-23-99, to allow for one of the controlled trials to be conducted in adolescents only. (The adolescent study, CN104141, was ongoing at that time.) This supplement was submitted 4-16-02, and the Pediatric Exclusivity Board granted BMS pediatric exclusivity for nefazodone on 6-27-02.

B. Important Issues with Pharmacologically Related Agents

To the best of my knowledge, there are none.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The sponsor has submitted a protocol for a juvenile animal study (in rats), but has not submitted the results.

III. Human Pharmacokinetics and Pharmacodynamics

Please refer to the review of study CN104136 by OCPB. As summarized in the sponsor's proposed labeling

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IV. Description of Clinical Data and Sources

A. Overall Data

The clinical data for this supplement come from 3 trials; one pharmacokinetic trial (CN104136) and two controlled efficacy trials (CN104141 and CN104187). In addition, study CN104141 includes a double blind extension phase of 26 weeks in duration, which is still ongoing; this submission contains data from the extension phase through 10-18-01. Similarly, study CN104187 has an open label extension phase up to 26 weeks in length which is also still ongoing; the supplement includes data from the open label phase through 12-21-01.

C. Table Listing the Clinical Trials

Study	Description
CN104136	Open label, 8 week pharmacokinetic study; nefazodone 50-300 mg/day (children) and 100-600 mg/day (adolescents); n=28; included long term open label followup treatment $\geq$ 18 weeks.
CN104141	Randomized, double blind, placebo controlled, multicenter, 8 week trial. Nefazodone 100-600 mg/day versus placebo; n=201 depressed adolescents. Double blind extension treatment of up to 26 weeks.
CN104187	Randomized, double blind, placebo controlled, multicenter, 8 week trial. Nefazodone 100-300 mg/day and 200-600 mg/day and placebo; n= 278 children and adolescents with depression. Open label follow up treatment of up to 26 weeks.

C. Postmarketing Experience

Although Serzone was approved in December 1994, the supplement does not include any postmarketing data for the pediatric population.

#### D. Literature Review

The supplement does not provide a literature review regarding use of nefazodone in the pediatric population.

#### V. Clinical Review Methods

The submission itself was the only source of clinical data for this review.

Because of the nature of this submission (i.e., it contains no positive efficacy studies upon which to base a labeling claim for pediatric use), it was decided at the 45-day filing meeting to forgo DSI inspection of the clinical sites.

Were Trials Conducted in Accordance with Accepted Ethical Standards? All studies were conducted in the U.S. and therefore were subject to the requisite IRB ethical oversight.

Evaluation of Financial Disclosure: BMS provided the required financial disclosure information under 21 CFR Part 54.2. None of the 47 investigators in these three studies had disclosable financial information. Two of the 358 subinvestigators made financial disclosures, but their financial interests did not appear to me to be improper with respect to the conduct of the study.

#### VI. Integrated Review of Efficacy

##### A. *Briefly* Present Conclusions and Any Critical Differences From Sponsor's Proposed Label Claims.

Although study CN104141 provided evidence for an effect of nefazodone on certain outcome measures (b) (4)

In study CN104187 there was no statistical evidence of a drug effect despite the fact that the sample size was roughly the same as in study CN104141. Thus no efficacy claim is warranted based on these trials, and in fact the sponsor is not seeking a claim.

##### B. General Approach to Review of the Efficacy of the Drug

Because the sponsor is not seeking any efficacy claim with this submission, it was decided at the 45 day filing meeting that no biometrics review would be necessary, and that this clinical review would be sufficient.

##### C. Detailed Review of Trials by Indication

## Study CN104141

Study conducted 10/29/98 – 9/19/01

### Investigators/sites:

Joshua Calhoun, MD Mercy Health Research, Chesterfield, MO  
Dennis Charney, MD; Andres Martin, MD, Yale University, New Haven, CT  
Graham Emslie, MD University of Texas Southwestern Medical Center, Dallas, TX  
Robert Findling, MD University Hospitals of Cleveland, Cleveland, OH  
Peter Londborg, MD Summit Research Network (Seattle) LLC, Seattle, WA  
Brian McConville, MD University of Cincinnati College of Medicine, Cincinnati, OH  
Deborah Deas, MD Medical University of South Carolina, Charleston, SC  
Murray H. Rosenthal, MD Behavioral and Medical Research, San Diego, CA  
Karen D. Wagner, MD, PhD University of Texas Medical Branch at Galveston, Galveston, TX  
Mora Ann Rynn, MD University of Pennsylvania, Philadelphia, PA  
Cynthia Pfeffer, MD New York Presbyterian Hospital, White Plains, NY  
Paras Harshawat, MD Comprehensive Psychiatric Practice, Terre Haute, IN  
J. Byron Stone, MD FutureSearch Trials, Austin, TX  
John Dunphy, MD Radiant Research – Eugene, Eugene, OR  
Randall Ricardi, DO Arizona Family Resource Counseling Center, Phoenix, AZ

Note: the sponsor did not provide the list of responsible IRBs in the submission, but offered to make this information available on request.

**Objectives:** The protocol states that the purpose of this study was to evaluate the safety and efficacy of nefazodone in adolescents.

**Population:** The subjects were to be healthy adolescents, aged 12-18 years, with a primary diagnosis of Major Depressive Episode. Subjects were to have a baseline CDRS-R score of at least 45. A wide variety of concomitant psychiatric diagnoses were exclusionary. Two hundred subjects were to be randomized to either placebo or nefazodone (in a 1:1 ratio). Amendment #2 to the protocol, dated 6-15-00, changed the upper age limit from 18 to 17 years.

**Design:** This was a multisite, randomized, double blind, parallel group, flexible dose, placebo controlled trial. The duration of double blind treatment was to be 8 weeks. Medication was to be administered BID with an initial dose of 50 mg BID, titrated to a maximum of 600 mg daily. Concomitant use of monoamine oxidase inhibitors, terfenadine, astemizole, triazolam, alprazolam, cisapride, clonidine, benzodiazepines, stimulants, other antidepressant drugs, and carbamazepine was prohibited.

**Assessments:** Screening assessments were to include history, physical exam, clinical laboratories, ECG, KSADS, CDRS-R, and HAMD. Efficacy measures included HAMD, CGI, CDRS-R, and safety monitoring assessments included vital signs, ECGs, and clinical laboratories.

(b) (4)

## Results

Of the 282 patients that were screened, 206 were randomized to treatment. The sponsor's table below shows the disposition of patients in the trial. There were slightly more discontinuations for lack of effect in the placebo group.

	Placebo	Nefazodone	Total
Randomized Sample	N = 100	N = 106	N = 206
Completed Study	59 (59)	75 (71)	134 (65)
Total Discontinuations	41 (41)	31 (29)	72 (35)
Lack of Efficacy	15 (15)	10 (9)	25 (12)
Patient Withdrew Consent	9 (9)	3 (3)	12 (6)
Lost to Follow-Up	4 (4)	8 (8)	12 (6)
Adverse Event <sup>a</sup>	3 (3)	6 (6)	9 (4)
Patient Unreliable	7 (7)	2 (2)	9 (4)
Other Known Cause	3 (3)	1 (1)	4 (2)
Pregnancy	0	1 (1)	1 (< 1)

Protocol CN104141

Source: Appendix 8.1B

<sup>a</sup> Patient CN104141-5-1151 was randomized to nefazodone, but was dispensed placebo. This patient is counted in the nefazodone group in this table.

**Demographics:** The median age for both the placebo and nefazodone groups was 15 years. The sample was 60% female, and the ethnic makeup was 78% Caucasian, 10% African-American, and 9% Hispanic.

**Dosing:** The mean nefazodone dose for completers was (b) (4).

**Primary Efficacy Measure:** (b) (4)

**Secondary efficacy measures:** (b) (4)

(b) (4)  
analysis used the complete sample of patients aged 12-18 years, or the slightly smaller sample of subjects aged 12-17 years.

**Conclusions:** This study provides some evidence that nefazodone is active in the treatment of adolescent major depressive disorder. However, the difference between placebo and nefazodone was only marginally statistically significant (b) (4)

## Study CN104187

Study conducted from 10-23-00 to 11-15-01

### Investigators/sites:

003 Scott Balogh, MD SouthEastern NeuroScience, Inc. Augusta, GA  
004 Joan Busner, PhD Penn State College of Medicine Hershey, PA  
005 Joshua Calhoun, MD Mercy Health Research St. Louis, MO  
006 Deborah Deas, MD Medical University of South Carolina Charleston, SC  
008 Anne Fedyszen, MD Dominion Clinical Research Midlothian, VA  
009 Robert Findling, MD University Hospitals of Cleveland Cleveland, OH  
010 Francine Friedman, MD Institute for Health Studies, Farmington Hills, MI  
011 Gary Gerard, MD Neurology Center of Ohio Toledo, OH  
012 Charles Grob, MD Harbor UCLA Research and Education Institute Torrance, CA  
013 Daniel Grosz, MD Pharmacology Research Institute Northridge, CA  
014 Jeffrey Hirschfield, MD Clinical Research of West Florida Clearwater, FL  
015 Alan Levine, MD Denver, CO  
016 Donna Palumbo, PhD University of Rochester Strong Memorial Hospital Rochester, NY  
017 Robert Reichler, MD Seattle, WA  
018 Moira Ann Rynn, MD University Science Center Philadelphia, PA  
019 Keith E. Saylor, PhD NeuroScience, Inc. Bethesda, MD  
020 Ward T. Smith, MD Summit Research Network Portland, OR  
021 Karen D. Wagner, MD Galveston, TX  
022 Karen L. Weihs, MD George Washington University Medical Center Washington, DC  
023 Carlos Figueroa, MD Advanced Psychiatric Group Rosemead, CA  
024 Paras Harshawat, MD Comprehensive Psychiatric Practice Terre Haute, IN  
028 J. Byron Stone, MD FutureSearch Trials Austin, TX  
029 John E. Dunphy, MD Radiant Research – Eugene Eugene, OR  
030 Randall Ricardi, DO Arizona Family Resource Counseling Center Phoenix, AZ  
032 C. Thomas Gualtieri, MD North Carolina Neuropsychiatry, PA Chapel Hill, NC  
033 James E. Lee, MD North Carolina Neuropsychiatry Charlotte, NC  
034 Marino Molina, MD Amedica Research Institute, Inc. Hialeah, FL  
035 Anjali Pathak, MD Ten Broeck Hospital of Jacksonville, Jacksonville, FL  
NB: The sponsor did not provide a list of the responsible IRBs, but this list is available from the sponsor on request.

**Objectives:** The purpose of this study was to demonstrate the efficacy of nefazodone administered in two dose ranges in children and adolescents with non-psychotic MDD.

**Population:** The subjects were to be physically healthy child and adolescent outpatients, aged 7-17, with MDD and a CDRS-R total score of at least 45. There were a number of Axis I psychiatric diagnoses that were exclusionary.

**Design:** This was a multisite, parallel group, randomized, double blind, placebo controlled trial. The duration of double blind treatment was 8 weeks, with optional open label extension treatment for 26 weeks. (b) (4)



Assessments: (b) (4), assessments were to include a history and physical exam, ECG, vital signs, clinical laboratories, pregnancy testing, K-SADS, CDRS-R, and urine drug screen. (b) (4)

Safety assessments included vital signs, clinical laboratories and ECGs. The protocol was amended (b) (4)

#### Results:

Patient disposition: The sponsor's table showing the disposition of the subjects is shown below.

	Placebo	Nefazodone Low	Nefazodone High
Randomized Sample	N = 94	N = 95	N = 95
Completed Study	71(76)	79(84)	67(70)
Total Discontinuations	23(24)	16(16)	28(30)
Withdrew Consent	5(5)	6(6)	8(8)
Lost to follow up	2(2)	4(4)	8(8)
Lack of Efficacy	6(6)	0	5(5)
Adverse Event	2(2)	5(5)	2(2)
Patient Unreliable	4(4)	0	3(3)
Other Known Cause	4(4)	1(1)	1(1)
Pregnancy	0	0	1(1)

Protocol CN104187

The low dose group had the highest percentage of patients completing the study.

Demographics: The mean age was approximately 12 years in all three dose groups, and all dose groups had approximately equal numbers of girls and boys. The sample was approximately 73% Caucasian, 10% African American and 11% Hispanic; there were no large imbalances in ethnic composition between treatment groups.

Dosing: The mean daily dose in mg by treatment group is shown below, for patients completing the trial.



(b) (4)

Efficacy results: The sponsor's table summarizing the primary efficacy measures is shown here.



(b) (4)

Conclusions: This study provides no evidence that nefazodone is active in the treatment of pediatric major depressive disorder.

## VII. Integrated Review of Safety

Brief Statement of Conclusions: Based upon these trials, the safety profile for nefazodone in the pediatric population does not appear to be significantly different from that in adults. Two nefazodone-treated subjects developed clinically significant rashes, but causality is difficult to assess.

Description of Patient Exposure ( i.e., number of patients at given duration, dose, demographic, distribution, country)

This supplement includes safety information on a total of 371 pediatric patients exposed to nefazodone (133 children and 238 adolescents). The sponsor's table below provides the details regarding the duration of exposure.

Study Interval (Days)	Number (%) of Patients		
	Children N = 133	Adolescents N = 238	All Nefazodone Patients N = 371
1 - 30	133	238	371
31 - 60	112	210	322
61 - 90	91	151	242
91 - 120	71	117	188
121 - 150	53	94	147
151 - 180	45	77	122
> 180	34	63	97

The demographic characteristics of the sample are shown in the following table, also taken from the submission.

Variable	Placebo <sup>a</sup>		Nefazodone		
	Children	Adolescents	Children	Adolescents	
N <sup>b</sup>	40	154	111	213	
Age (years)	Mean	9.6	14.7	9.5	14.7
	Median	10.0	15.0	9.0	15.0
	Minimum-Maximum	7.0 - 11.0	12.0 - 18.0	7.0 - 12.0	12.0 - 18.0
	SE	0.2	0.1	0.1	0.1
Gender N (%)	Boys	24 (60)	59 (38)	66 (59)	89 (42)
	Girls	16 (40)	95 (62)	45 (41)	124 (58)
Race N (%)	White	33 (83)	124 (81)	84 (76)	150 (70)
	Black	4 (10)	9 (6)	10 (9)	29 (14)
	Hispanic/Latino	2 (5)	12 (8)	9 (8)	25 (12)
	American/Alaskan Native	0	1 (1)	0	2 (1)
	Asian/Pacific Islander	0	3 (2)	0	1 (0)
	Other	1 (3)	5 (3)	8 (7)	6 (3)

Note that there were more boys among the children, but more girls in the adolescent age group. The ethnic makeup of the sample was predominantly Caucasian.

### C. Methods and Specific Findings of Safety Review

Deaths and Serious Adverse Events: There were no deaths in these trials. There were a total of 8 serious adverse events among nefazodone treated children and adolescents in these trials, as listed below. In addition, there were 2 serious adverse events during placebo treatment.

#### Nefazodone

- Nefazodone overdose (2 subjects)
- Psychosis
- Tonsillectomy
- Suicide attempt
- Worsening of depression

#### Placebo

- Hostility
- Asthma

Also, 2 adolescent girls became pregnant while receiving nefazodone; the outcome of one pregnancy was not known at the time of the submission, and the other pregnancy was terminated by an elective abortion.

Adverse Dropouts: The sponsor provided only a listing of the adverse events that were associated with premature discontinuation. By inspection, the adverse events most often associated with dropout during the short term trials were insomnia and rash (accounting for discontinuation by 3 nefazodone-treated patients each).

The cases of discontinuation for rash merit some further description. Patient 002-008 in study 136, a 12 year old girl, developed a rash after 5 days of nefazodone treatment; the rash was pruritic and papular, with some desquamation, and involved the trunk, axilla and lower extremities. The rash resolved after nefazodone was discontinued. In study 187, patient 21-410, a 9 year old girl, developed a “full body rash” after 12 days of nefazodone treatment; the rash resolved after the drug was stopped. Patient 6-1055 in study 141, an 18-year old female, discontinued nefazodone after 6 days because of headache and a “mild rash” that was not further characterized. Additionally, subject 2-1155 in the same trial, an 18-year old female, discontinued nefazodone for itching, although no rash was mentioned.

There was one dropout for elevated liver enzymes (patient 21-325 in the extension phase of study 187). This subject, an 11 year old male, developed asymptomatic liver enzyme elevations (LDH 471 U/L, AST 96 U/L, ALT 123 U/L) and discontinued treatment. Follow-up liver enzymes were not obtained but the patient was reported to have remained asymptomatic. (Treatment with nefazodone has been associated with hepatotoxicity in adults, as described in the Serzone labeling.)

Common adverse event profile: Data from the placebo controlled trials is summarized below.

Adverse events that were statistically significantly more frequent with nefazodone than placebo:

- headache
- nausea
- dizziness
- abnormal vision (all events were in adolescents)

Adverse events meeting criteria for being “common and drug-related” (RR  $\geq$ 2, incidence  $\geq$  5% with nefazodone):

- nausea
- dizziness
- cough increased

With respect to demographic subgroups, the sponsor examined the incidence of adverse events by age category, gender and ethnicity. In general, females reported more adverse events than males, and adolescents reported more adverse events than children. Since the large majority of subjects were Caucasian, it was difficult to provide meaningful comparisons of adverse events between ethnic groups. On balance, no adverse events appeared to be unique to a specific demographic group.

Clinical laboratories: The sponsor defined clinical laboratory values of potential clinical significance and determined the number of subjects who met such criteria following study treatment. There was one finding that showed a more frequent abnormality among the nefazodone subjects: five nefazodone subjects (but no placebo subjects) in short term trials had treatment-emergent low hematocrit or hemoglobin. In the extension phase of study 187, an additional nefazodone patient had treatment-emergent low hematocrit. The clinical significance of this finding is unclear.

Vital signs: The sponsor compared the incidence of potentially clinically significant vital sign abnormalities between nefazodone and placebo groups in the controlled trials (n= 193 for placebo and n=314 for nefazodone). The parameters analyzed included blood pressure, heart rate and weight. The biggest between-treatment discrepancies in the incidence of abnormalities were for increased systolic blood pressure (in 4.1% of nefazodone patients compared to 0.5% of placebo patients) and for decreased diastolic blood pressure (in 8.3% of nefazodone patients and 3.1% of placebo patients).

Electrocardiograms: The sponsor established criteria for potentially clinically significant ECG abnormalities for selected parameters (heart rate, PR, QRS, QTc, etc.; please refer to ISS Table S.5.3.6.2B). <sup>(b) (4)</sup> two nefazodone treated subjects but no placebo subjects had treatment-emergent QTc values <sup>(b) (4)</sup> that were also <sup>(b) (4)</sup> increased over baseline. Other treatment-emergent ECG abnormalities in nefazodone patients included sinus bradycardia, supraventricular premature beats, incomplete RBBB, and ectopic atrial rhythm.

At the Division's request, the sponsor also provided an analysis of central tendency for heart rate, PR, QRS, QT, RR and QTc. Michael Eison of BMS submitted these data via email 8-19-02. The sponsor analyzed data from both the long term and the short term phases of studies 141 and 187, pooling the drug and placebo patients. (b) (4)

However, there were no statistically significant differences between nefazodone and placebo by analysis of least square means (data not shown). On balance, there was not evidence for an effect of nefazodone on ECG parameters in these trials.

Literature review: None was provided in the submission.

#### C. Adequacy of Safety Testing

The sponsor did not provide an analysis of central tendency (i.e., mean or median changes from baseline) for vital signs, weight, or clinical laboratory parameters. In other respects the safety testing was adequate.

#### E. Summarize Critical Safety Findings and Limitations of Data

There are no safety findings, in my opinion, that would warrant inclusion in the Serzone label. The most significant limitation of these data is the lack of information on the long-term effects of nefazodone, with respect to growth and development.

#### VIII. Dosing, Regimen, and Administration Issues

As no pediatric claim is to be made, there are no relevant issues.

#### IX. Use in Special Populations (it is mandatory to fill this section out)

This supplement is limited to data in the pediatric population.

#### X. Conclusions and Recommendations

The adolescent trial (141) demonstrated some evidence for activity of nefazodone in the treatment of pediatric depression (b) (4)

Study 187, with both children and adolescents as subjects, did not show any effect of nefazodone relative to placebo; in fact, the outcome for the placebo group was numerically superior to the high dose group.

With respect to the timing and conduct of the two studies, it is interesting to note that study 141, (b) (4) was initiated prior to the pediatric exclusivity Written Request, and involved 15 sites. It was conducted between October 1998 and September 2001. In contrast, study 187 was initiated after the pediatric exclusivity Written Request, and despite the fact that it involved a larger sample it was completed in approximately one-third the time (October 2000 to November 2001). With 28 sites, study 187 had almost twice as many investigators as study 141. Speculatively, the need for the sponsor to complete study 187 rapidly to meet the deadline for the Written Request may have introduced a certain lack of precision into the conduct of the trial.

With respect to safety, there were no adverse reactions evident in these trials that would be of unique concern for the pediatric population. There were two clinically significant cases of rash that may have been drug-related, but causality is difficult to assess.

In my view, no labeling changes are necessary for Serzone based on these trials. The efficacy trials were uninformative since they failed to show a separation between nefazodone and placebo, and there are no unique pediatric safety issues that need to be incorporated in the labeling. Accordingly, I recommend (b) (4) for this supplement.

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/s/

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Andy Mosholder  
9/6/02 01:10:14 PM  
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Thomas Laughren  
9/6/02 01:26:28 PM  
MEDICAL OFFICER

I agree that this supplement (b) (4) see  
memo to file for more detailed comments.--TPL