REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 20-152
SUPPLEMENT: S-032
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 a "not approvable" action 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: The primary outcome measure was the change from baseline in the CDRS-R total score. The results are shown below. Separation between nefazodone and placebo was not demonstrated, and in fact the mean improvement for the placebo group was numerically superior to that of the high dose group.

Treatment	N	Baseline	Mean change from baseline	p-value vs. placebo
Placebo	93	58.3	-21.6	-
Low dose	90	61.2	-23.2	0.43
High dose	90	61.0	-20.6	0.65

Study 141: The primary outcome measure was the change from baseline in CDRS-R (the first 17 items). The mean change from baseline on the CDRS-R total score at endpoint was –25.8 for nefazodone patients and –22.1 for placebo patients (p-value = 0.077).

Secondary outcome measures included the CGI improvement response rate, with response defined as a score of 1 or 2, and the HAMD total score. The percent of patients meeting the aforementioned criteria for response on the CGI was 63% for nefazodone and 44% for placebo (p-value = 0.004). On the HAMD total score, the mean change from baseline to final visit was –9.9 for nefazodone and –8.0 for placebo (p-value = 0.025).

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 on the CDRS-R, the primary outcome measure. Therefor, 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.