Clinical Pharmacology and Biopharmaceutics Review

sNDA: 20-152/SE5-032 **Submission Date: 04/16/2002**

Type of Submission: Pediatric labeling supplement

Drug Name: Nefazodone (Serzone®)

Indication of Drug: Treatment of depression

Formulation: Oral tablets (50, 100, 150, 200, and 250 mg)

Sponsor: Bristol-Myers Squibb Company
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1. Executive Summary

This pediatric labeling supplement consists of one pharmacokinetic study (Protocol No. CN104136) with the title 'An open-label pharmacokinetic trial of nefazodone in depressed children and adolescents.' The 8-week short-term phase of the 26-week open-label, two-center, non-randomized single sequence Phase 2 study design included a 2-week pharmacokinetic evaluation in depressed pediatric patients. The 8 week trial period is the focus of this report. For comparison the results of this study were contrasted to healthy adults which were assessed in a different trial (Protocol No. CN104068).

Pharmacokinetic parameters for nefazodone (NEF) and its three primary metabolites hydroxy-nefazodone (HO-NEF), meta-chlorophenylpiperazine (mCPP), and a triazole-dione metabolite (DIONE) were assessed in children and adolescents. Only the area under curve (AUC) and the maximum of plasma concentration (Cmax) were taken into further evaluation. The following two summary tables (Table 1) show relative mean AUC values (Table 1A) and relative mean Cmax values (Table 1B) with their respective 95% confidence intervals, for NEF and its metabolites HO-NEF, mCPP, and DIONE with respect to healthy adults (Protocol No. CN104068):

Table 1A. Dosing of 100 mg NEF BID at steady-state			
Population	**Adult[a]**	**Child[b]**	**Adolescent[b]**
	Mean[c] (95%-CI[d])	**Mean[c] (95%-CI[d])**	**Mean[c] (95%-CI[d])**
AUC(TAU) (h·ng/mL)			
/Analyte			
NEF	1 (1.53, 1.82)	1.82 (1.12, 2.52)	0.79 (0.30, 1.29)
HO-NEF	1 (0.49, 1.51)	1.55 (0.98, 2.11)	0.71 (0.31, 1.11)
mCPP (extensive metabol.[e])	1 (0.82, 1.18)	1.87 (0.75, 2.99)	0.98 (0.67, 1.30)
DIONE	1 (0.79, 1.21)	1.63 (1.30, 1.97)	1.10 (0.88, 1.32)

Table 1B. Dosing of 100 mg NEF BID at steady-state			
Population	**Adult[a]**	**Child[b]**	**Adolescent[b]**
	Mean[c] (95%-CI[d])	**Mean[c] (95%-CI[d])**	**Mean[c] (95%-CI[d])**
Cmax (h·ng/mL)			
/Analyte			
NEF	1 (0.70, 1.30)	1.76 (1.11, 2.41)	0.61 (0.35, 0.87)
HO-NEF	1 (0.73, 1.11)	1.48 (0.98, 1.97)	0.60 (0.38, 0.82)
mCPP (extensive metabol.[e])	1 (0.85, 1.15)	1.80 (1.10, 2.55)	1.00 (0.80, 1.20)
DIONE	1 (0.82, 1.18)	1.52 (1.21, 1.83)	0.99 (0.80, 1.18)

[a]: healthy volunteers (CN104068)
[b]: depressed patients (CN104136)
[c]: mean, relative to adults
[d]: confidence interval, relative to mean
[e]: only for phenotyped CYP2D6 extensive metabolizers

In general, exposure (AUC, Cmax) to NEF and its metabolites were higher in children compared to adolescents or adults, while exposure values in adolescents were similar to those in adults. A number of similarities in the pharmacokinetics of nefazodone in adults and the two pediatric age groups were observed: the rank order of plasma concentrations of nefazodone metabolites was maintained, and terminal elimination half-lives of each analyte were similar among age groups.

(b)(4)