Clinical Pharmacology and Biopharmaceutics Review

sNDA: 20-152/ (b) (4) **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
5 Research Parkway
Wallingford, CT 06492

Reviewer: Carl-Michael Staschen, M.D., Ph.D.

Team Leader: Raman K. Baweja, Ph.D.

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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):

(b) (4)

In general, exposure (AUC, Cmax) to NEF and its metabolites were (b) (4) 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.

We recommend the following changes in the package insert:
Under CLINICAL PHARMACOLOGY, in subsection Pharmacokinetics add:

(b) (4)

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2. Labeling comments to the sponsor

Based on results from study report CN104136 you propose the following label change in the revised text (PRECAUTION section). FDA proposes a revised version. OCPB recommends that the sponsors text can be modified and the scientific context is better placed under the CLINICAL PHARMACOLOGY/Pharmacokinetic section. Since each patient will be individually titrated, description of the results of this study in the pharmacokinetic section are adequate, and therefore, there is no need to place any concern in the PRECAUTION section of the package insert. The following Table 2 compares the sponsor's current and submitted label revision as well as FDA's proposal.

Table 2. Package Insert		
Sponsor		**FDA**
Section PRECAUTIONS		**Section CLINICAL PHARMACOLOGY**
Current	**Submitted Revision**	**Proposal**
Safety and effectiveness in individuals below 18 years of age have not been established.	(b) (4)	

FDA's reasoning for the revision is as follows:

- It is not known what the differences between children and adolescents regarding AUC and Cmax would have been if they would have been measured at the highest administered dose.

Recommendations: The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed this submission and has the labeling comments as described above. Please forward these comments to the sponsor.

Signatures:

1. Carl-Michael Staschen, M.D., Ph.D. _____

2. Raman Baweja, Ph.D. _____
   Div. of Pharm. Eval.–I, OCPB

CC: sNDA 20-152/ (b) (4) HFD 120, HFD 860 (Mehta, Sahajwalla, Baweja, Staschen), Central Document Room (Biopharm-CDR)

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3. Summary of Clinical Pharmacology and Biopharmaceutics and Question Based Review

This is a review of a proposed pediatric exclusivity determination request and a revision of label for nefazodone (Serzone®), an oral antidepressant - PRECAUTIONS: (b) (4)

The sponsor has submitted draft labeling to update the PRECAUTIONS: (b) (4) section with additional information for nefazodone hydrochloride (Serzone®) tablets (NDA 20-152) regarding the pharmacokinetics of nefazodone and its metabolites in children and adolescents.

The label revision was initiated and requested by the Sponsor (letter dated 03/4/1999). The new proposed revisions to the label provide new safety and pharmacokinetic data with regard to Serzone® in pediatric patients and fulfills the sponsor's Phase 4 clinical commitment to conduct and submit results from studies to evaluate the use of nefazodone in children and adolescents with depression, as described in the Serzone® approval letter dated December 22, 1994. The revisions derive from three new clinical investigations that studied nefazodone in pediatric populations with major depressive episode. Two studies investigated the safety and efficacy of nefazodone in pediatric populations (one study, CN104141, in adolescents only; the other, CN104187, in children and adolescents) while another study investigated the pharmacokinetic of nefazodone in both age groups (CN104136).

1. What is the proposed mechanism of action ?

(b) (4)

2. What are the pharmacokinetic characteristics ?

Orally administered nefazodone is rapidly and completely absorbed, with peak plasma concentrations occurring 1 to 3 hours after dosing. Food delays the absorption of nefazodone and decreases its bioavailability by approximately 20%. Peak plasma nefazodone concentrations are reached at about one hour after oral administration and steady state concentrations are achieved within 4 to 5 days of initiation of therapy. The drug has a large volume of distribution (0.22 to 0.87 L/kg) and is highly (> 99%) but loosely bound to plasma proteins.

Nefazodone has a short mean elimination half-life of 2 to 4 hours, indicating removal is prompt following withdrawal. Like other antidepressants, nefazodone is metabolized in the liver, and the pharmacokinetics of three of its metabolites have been determined. A major active metabolite is hydroxy-nefazodone, with an area under the curve (AUC) approximately 40% that of the parent compound and a similar half-life (1.5-4.0 hours) and pharmacologic profile. The pharmacologic profile of the other major metabolite, triazole-dione, has not yet been well characterized. The AUC for the triazole-dione metabolite is approximately four times that of the parent compound, with an elimination half-life of approximately18 hours. Meta-chloro-phenylpiperazine (mCPP) is a minor active metabolite, with an AUC approximately 7% that of the parent compound and a half-life of 48 hours.
Less than 1% of the administered dose of nefazodone is excreted in urine as unchanged drug. Approximately 55% is excreted in urine and about 20%-30% in feces.

Both nefazodone and its pharmacologically similar metabolite HO-NEF exhibit nonlinear kinetics for both dose and time with AUC and Cmax increasing more than proportionally with dose increases and more than expected upon multiple dosing over time, compared to single dosing. The metabolites mCPP and DIONE have apparent dose linearity.

While the pharmacokinetics of nefazodone are unaltered in patients with renal impairment (creatinine clearance 7-60 mL/min/1.73 m^2), plasma concentrations and half-lives of nefazodone and hydroxy-nefazodone are increased in the elderly and in patients with hepatic dysfunction as a result of decreased metabolic clearance. It is therefore recommended that the initial dose of nefazodone be 50 mg twice daily and dose titration be slower in the latter two groups of patients. The final target dose for the elderly is based on careful assessment of the patient's clinical response. In controlled clinical trials, the effective dose range for nefazodone was generally 300-600 mg/day for all patients.

3. *What are the enzymes involved in the metabolism of nefazodone?*

Nefazodone (NEF) is extensively metabolized in humans and has a potential for drug interactions with the hepatic cytochrome P-450 isoenzyme system (CYP). Of the known metabolites of nefazodone, hydroxy-nefazodone (HO-NEF) and the triazole-dione (DIONE) metabolite are pharmacologically active and may contribute to the therapeutic activity of nefazodone. m-Chlorophenylpiperazine (mCPP) shows weak activity. In-vitro, the cytochrome P450 (CYP) isozyme CYP3A4 is primarily responsible for the metabolism of NEF, HO-NEF, and DIONE while mCPP is primarily metabolized by CYP2D6. Nefazodone is also a weak inhibitor of CYP3A4. The pharmacokinetics of mCPP but not NEF or the other metabolites, exhibits genetic polymorphism which segregates with dextromethorphan phenotype.
The following scheme (Figure 1) shows the proposed metabolic pathway for nefazodone in humans.

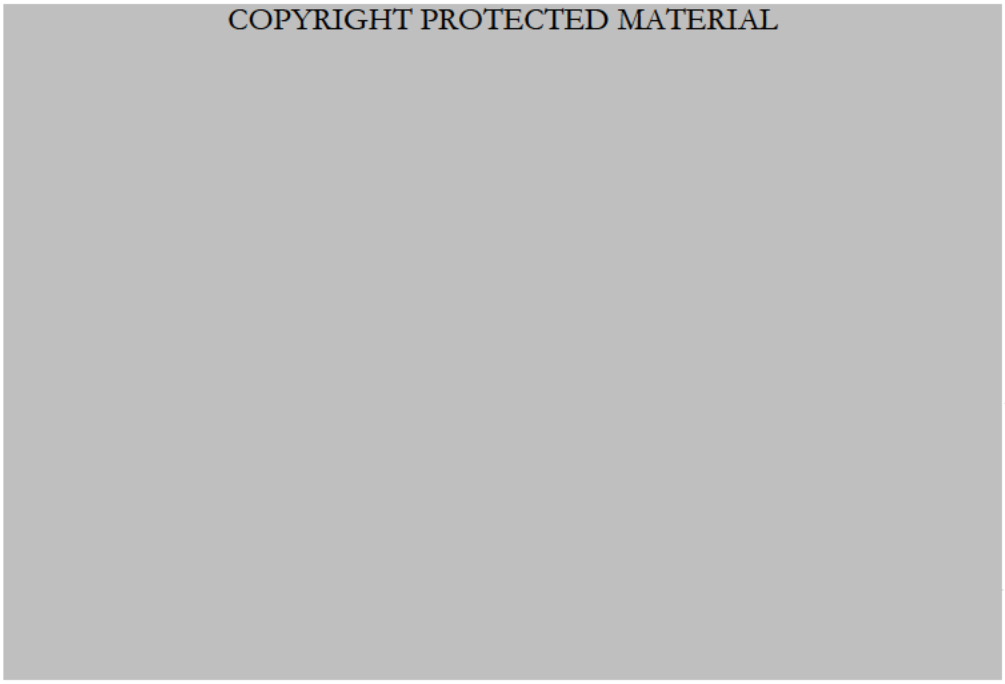


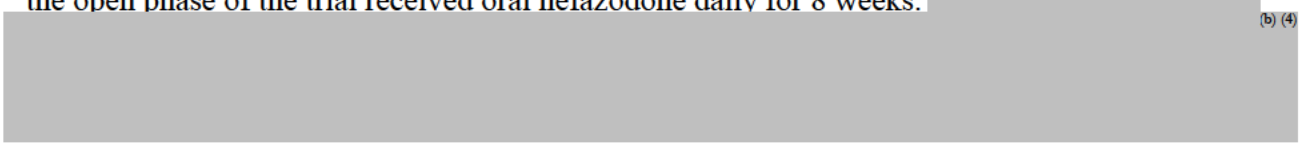
Figure 1
Proposed metabolic scheme for nefazodone in humans, Specific cytochrome P450 isozymes responsible for metabolism of individual compounds are denoted. Apparent primary metabolic pathways are shown with boldface arrows. (Findling R.L. et al., J. Am. Acad. Child Adolesc. Psychiatry 39: 1008-1016, 2000)

4. *What are the PK/PD relationships ?*

So far there has been no attempt to elucidate a concentration-response relationship for nefazodone due to the high intra- and interindividual variability as well as the contribution of nefazodone's active metabolites to its therapeutic response.

Study report (CN104136)
Title: 'An open-label pharmacokinetic trial of nefazodone in depressed children and adolescents.'

Briefly, the 8-week short-term phase of the 26-week CN104136 study was an open label, non-randomized, two-center single sequence study design. The short-term phase is the focus of this report. Twenty-eight (28) patients at two study centers, 15 children (ages 7 to 12 yr) and 13 adolescents (ages 13 to 16 yr), diagnosed with major depression, were enrolled in the CN104136 study. Following a 1- to 4-week drug-free baseline evaluation period, patients who qualified for the open phase of the trial received oral nefazodone daily for 8 weeks. (b) (4)



(b) (4)

(b) (4) Of the patients enrolled, 13 children and 13 adolescents had complete blood sampling and were included in the evaluation of pharmacokinetics.

The pharmacokinetic parameters obtained were Cmax, Tmax, AUC, T-HALF , and AUCR. Tmax is the time of the observed maximum concentration (Cmax). AUC(INF) is the area under the plasma concentration-time curve from time zero extrapolated to infinity, and was calculated following Day 1 dosing. AUC(TAU) is the area under the plasma concentration-time curve over the dosing interval, and was calculated following Day 7 and Day 14 dosing. T-HALF is the terminal half-life. AUCR compares the AUC values of the metabolites to the parent compound. In Table 3, these values are contrasted to those from a study in healthy adults (CN104068) who were dosed 100 mg of nefazodone BID for 10 days. Comparisons to adults, and between children and adolescents, were made by comparison of arithmetic mean values, and not statistically based.

In general, exposure to NEF and its metabolites (as measured by Cmax and AUC) (b) (4) in children compared with adolescents or adults (see also Table 3).

(b) (4)

The rank order of metabolite plasma concentrations (DIONE > NEF > HO-NEF > mCPP) was maintained in both children and adolescents. Terminal elimination half-lives of NEF and metabolites in the two age groups were similar to those in adults (about 4 hours). NEF and HO-NEF showed evidence of nonlinearity in their pharmacokinetics as indicated by accumulation at steady state that could not be predicted based on single dose data, and by a more than dose proportional increase in AUC at steady state. The extent of nonlinearity in the pharmacokinetics of NEF and HO-NEF in children and adolescents appeared to be similar to that in adults.

Table 3
Pharmacokinetic parameter values for Nefazodone (NEF) and metabolites in children and adolescents (Protocol No. CN104136) compared to those in adults (Protocol No. CN104068). For more information see text.

A correlation analysis relating pharmacokinetic exposure parameters (Cmax, AUC) to body weight combining two trials (juvenile patients and healthy adults) showed that Cmax of nefazodone (b) (4) hydroxy-nefazodone (b) (4) and DIONE (b) (4) were significantly correlated with the patients body weight. However, only AUC(TAU) of DIONE showed a significantly correlation with body weight (b) (4)

Safety assessments revealed no evidence that nefazodone treatment resulted in organ toxicity. The adverse event profile seen in children and adolescents in this trial was qualitatively similar to that of adults.

Conclusions:

As a final conclusion OCPB confirms the sponsors interpretation of the results. However, the proposed label change regarding nefazodone is modified to include the information of expected changes in AUC and Cmax when administered to pediatric patients.

4 Final Study Report: Protocol CN104-136:

'An open-label pharmacokinetic trial of nefazodone in depressed children and adolescents'

Study Objectives:

- To evaluate the safety and pharmacokinetics of nefazodone in children and adolescents with depression.
- A secondary objective was to obtain preliminary efficacy data for these age groups.

Study Design:

This was an open-label, two-center, fixed sequence, multiple dose study in which 2 treatment groups (Groups A and B) of 15 pediatric patients each were evaluated. The treatment regimen, as well as the pharmacokinetic assessments performed for each group are summarized below in Figure 2.

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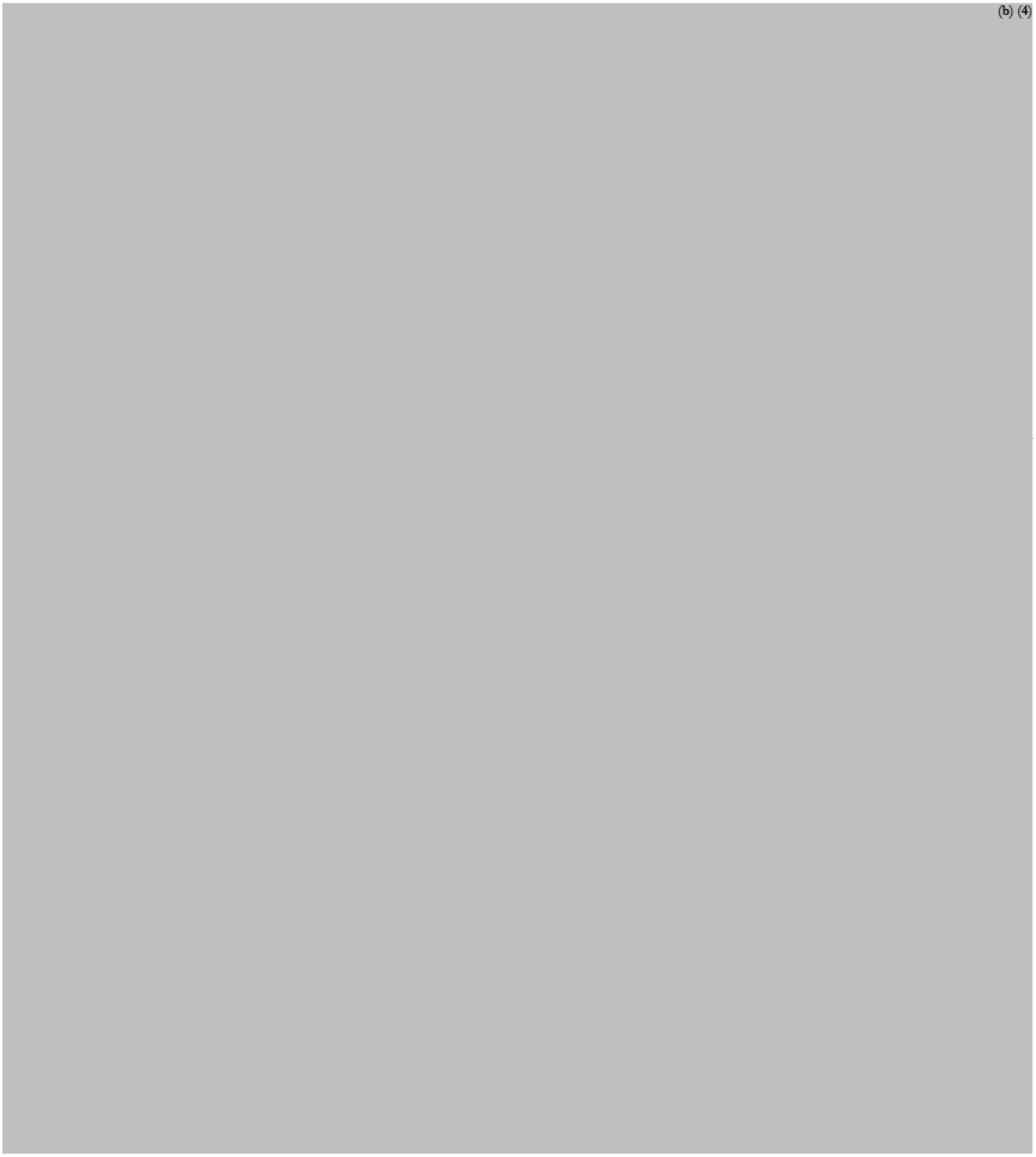


Figure 2
Schematic of study design for "an open–label pharmacokinetic trial of nefazodone in depressed children and adolescents". Nefazodone Protocol CN104-136.

Evaluation Groups:

A total of 28 patients were enrolled at two study centers in the USA from March 5, 1996 to September 26, 1996. Each center enrolled 14 patients. Demographic characteristics of the total sample are summarized by age group and compiled in Table 4.

Characteristic		Children N = 15	Adolescents N = 13	Total N = 28
Age (years)	Median	10	14	12
	Range	7 - 12	13 - 16	7 – 16
Sex	Boys	7	5	12
	Girls	8	8	16
Race	White	15	10	25
	Black	0	2	2
	Other	0	1	1
Weight (lbs)	Median	97	138	112
	Range	64 - 171	95 - 286	64 - 286
Tanner Stage	1	11	0	11
	2	4	0	4
	3	0	4	4
	4	0	6	6
	5	0	3	3

Table 4
Demographic characteristics of depressed children and adolescents (Nefazodone Protocol CN104-136)

Observations excluded

Patients 002-007 and 002-008 from the children stratum were excluded from the pharmacokinetic sample. Patient 002-007 had a pretreatment blood sample collected on Day 1 but refused to have any further blood sampling done. Patient 002-008 had serial blood samples collected on Day 1 but discontinued from the study after 5 days of treatment. Although this patient was excluded from summary statistics of pharmacokinetic parameters, data were included in the computation of mean concentrations on Day 1. In addition, available individual pharmacokinetic parameter values for this patient are presented in the report.

Pharmacokinetic Evaluation:

Patients who meet the entrance criteria were participating in a baseline phase of one to four weeks. Patients who at the end of baseline continue to meet criteria were beginning treatment with nefazodone. All patients were initially treated with a daily dose of 100 mg of nefazodone (50 mg BID). Blood samples were collected at specific times during this trial for the purpose of measuring nefazodone and its metabolites, hydroxy-nefazodone, meta-chlorophenylpiperazine, and a triazole-dione metabolite. On day 1, blood samples were collected at 0 (predose), 0.5, 1,2, 4, 6, 8 and 12 hours after dosing.

While this is an outpatient trial, the option to confine patients for the first five days of treatment was available. A single blood sample to measure trough levels of nefazodone and its metabolites was collected immediately before dosing on the two days preceding the steady state

pharmacokinetic sampling at the End of Week 1 and at the End of Week 2. Steady state blood samples were collected at 0 (predose), 0.5, 1, 2, 4, 6, 8 and 12 hours after dosing at the End of Week 1 and again at the End of Week 2. On day 9, the dose of nefazodone was titrated to 200 mg daily for all patients.

The following pharmacokinetic parameters were derived for nefazodone and its metabolites from the plasma concentration vs. time data for each subject

Cmax (ng/mL)	Maximum observed plasma concentration after the dose
Tmax (hr)	The time required to reach Cmax
AUC(INF) (ng·hr/ml)	Area under the concentration versus time curve from 0 to infinity
AUC(0-t) (ng·hr/ml)	Area under the concentration versus time curve from 0 to the last measurable time point
AUC(TAU) (ng·hr/ml)	Area under the concentration versus time curve over the dosing interval (0-12 hr)
T-HALF (hr)	Plasma elimination half-life

Analytical Methods:

Plasma samples were assayed for NEF and its metabolites, OH-NEF, mCPP, and DIONE, by a validated HPLC-UV method. The lower limits of quantification (LLQ) and the upper limit of quantification (ULQ) as well as precision and accuracy are compiled in Table 5.

Overall evaluation of the analytical methods with respect to precision and accuracy is acceptable.

Statistical Methods:

Pharmacokinetic parameters of nefazodone and its principle metabolites are tabulated and summary descriptive statistics are calculated by sampling time and age group. Ninety five percent (95%) confidence bounds were constructed around the mean parameter estimates.

Results:

Pharmacokinetics of Nefazodone and Metabolites

Given the long half-life of DIONE and the short sampling time of 12 hours post dose, a reliable estimate of T-HALF could not be obtained; therefore, trapezoidal AUC up to 12 hours after the first dose was used in the analysis, and AUC(INF) and T-HALF values were not calculated for this metabolite. Since the predose samples prior to the end of Week 1 and end of Week 2 sampling were not obtained precisely at 12 hours from the previous dose, measured concentrations in those samples cannot be regarded as the CMIN samples. Therefore, attainment of steady state in plasma concentrations of NEF and its metabolites could not be verified. Based on knowledge in adults, it is assumed that a steady state was reached within 7 days of BID dosing with NEF. Figures 3 – 6 compare AUC, Cmax, Tmax and T-HALF between different populations and different dosing schemes. Results are compiled in Tables 6A-C.

Patients 001-004 and 001-007 from the children stratum and Patients 001-003, 002-005, and 002-009 from the adolescent stratum were determined to be poor metabolizers based on the urinary ratio of dextromethorphan to dextrorphan. Since the oxidative metabolism of mCPP is known to be mediated by cytochrome P450 2D6, summary statistics of pharmacokinetic variables for mCPP is reported with and without these five poor metabolizers (Tables 6C)

Pharmacokinetics after a single dose.

Following a single dose of 50 mg, quantifiable plasma concentrations of NEF were observed only in a few samples (b) (4) see also Table 6A. As a result, T-HALF and AUC(INF) could be estimated in only 7 of 13 children and 1 of 13 adolescents. Plasma concentrations of HO-NEF (b) (4) and mCPP (b) (4) were also below quantifiable limits in a majority of the samples collected, The DIONE metabolite (b) (4) had the highest plasma concentrations of all the analytes and was quantifiable up to 12 hours after treatment in all patients after the 50-mg single dose of NEF. Plasma concentrations of all analytes were (b) (4) in children compared with adolescents.

Pharmacokinetics at steady state.

Plasma concentrations of NEF, HO-NEF, and DIONE were about (b) (4) at steady state in comparison to the single dose, plasma concentrations of mCPP at steady state were comparable to those after the single dose. Exposure to NEF and HO-NEF, as determined by AUC, more than doubled with a (b) (4) in dose while exposure to mCPP and DIONE showed (b) (4) in relation to dose. Cmax and AUC values for NEF and its metabolites were (b) (4) in children compared with adolescents. Elimination half-lives (T-HALF) for all analytes were (b) (4) in children and adolescents. Although T-HALF for DIONE could not be accurately determined, it appeared to be the longest of all analytes in both children and adolescents.

For NEF, poor correlations were found at steady state after 100 mg BID dosing between body weight and AUC(TAU), and body surface area and AUC(TAU). Combined data from the two age groups yielded a correlation coefficient (b) (4) for body weight and (b) (4) for body surface area.

Pharmacokinetics in extensive vs. poor metabolizers.

Patients 001-004 and 001-007 in the children stratum, who were classified as poor metabolizers, showed pharmacokinetic values similar to others for NEF, HO-NEF, and DIONE. For mCPP, T-HALF and AUC values were (b) (4) in these patients with the AUCR values distinctly (b) (4) than all other patients (see also Table 6C).

In the adolescent stratum, Patients 001-003 and 002-009, who were also classified as poor metabolizers, showed no differences in pharmacokinetic parameters compared with others for NEF, HO-NEF and DIONE. Patient 002-005, another poor metabolizer, showed (b) (4) exposure to NEF and HO-NEF compared with other patients. Exposure to mCPP was (b) (4) in all adolescents classified as poor metabolizers (see also Table 6C). The AUCR values for mCPP were also (b) (4) for patient 001-003 and Patient 002-009; however, the AUCR value for Patient 002-005 (b) (4) was (b) (4) of other patients since the exposure to NEF was also (b) (4) in this patient.

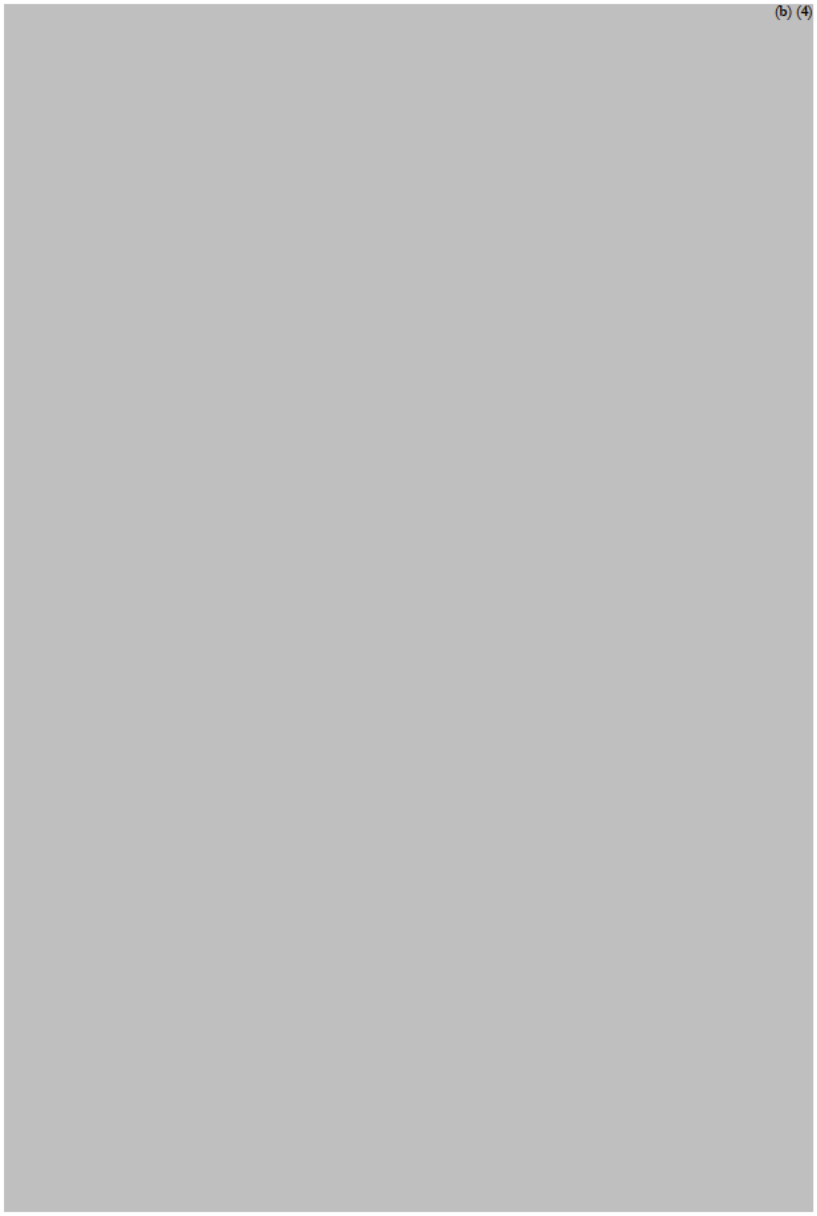
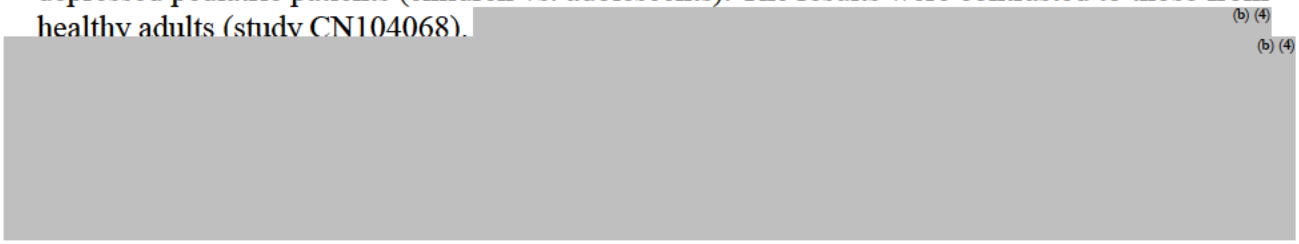


Figure 3

Pharmacokinetic exposure parameter of Nefazodone (NEF) and its primary metabolites in depressed pediatric patients (children vs. adolescents). The results were contrasted to those from healthy adults (study CN104068).



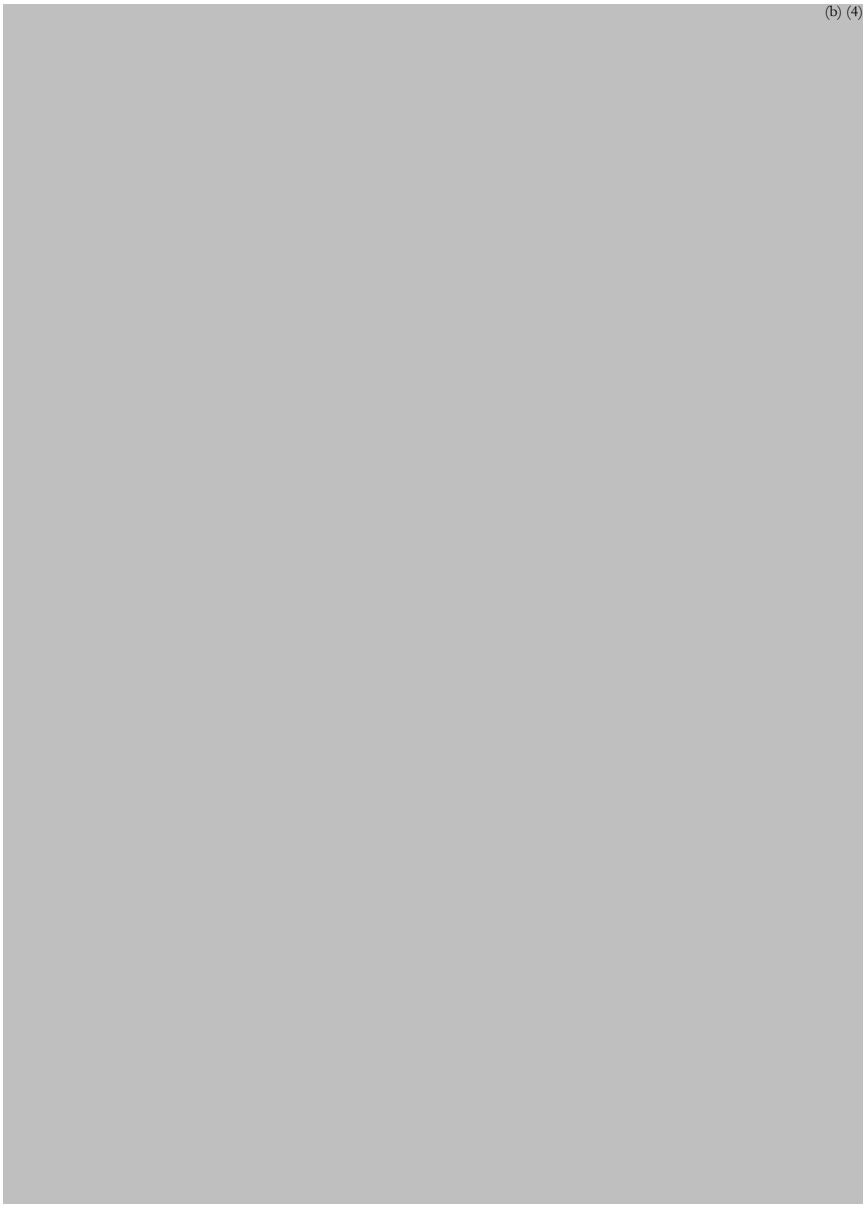


Figure 4

Pharmacokinetic exposure parameter of Nefazodone (NEF) and its primary metabolites between depressed pediatric patients (children vs. adolescents). The results were contrasted to those from healthy adults (study CN104068)

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(b) (4)

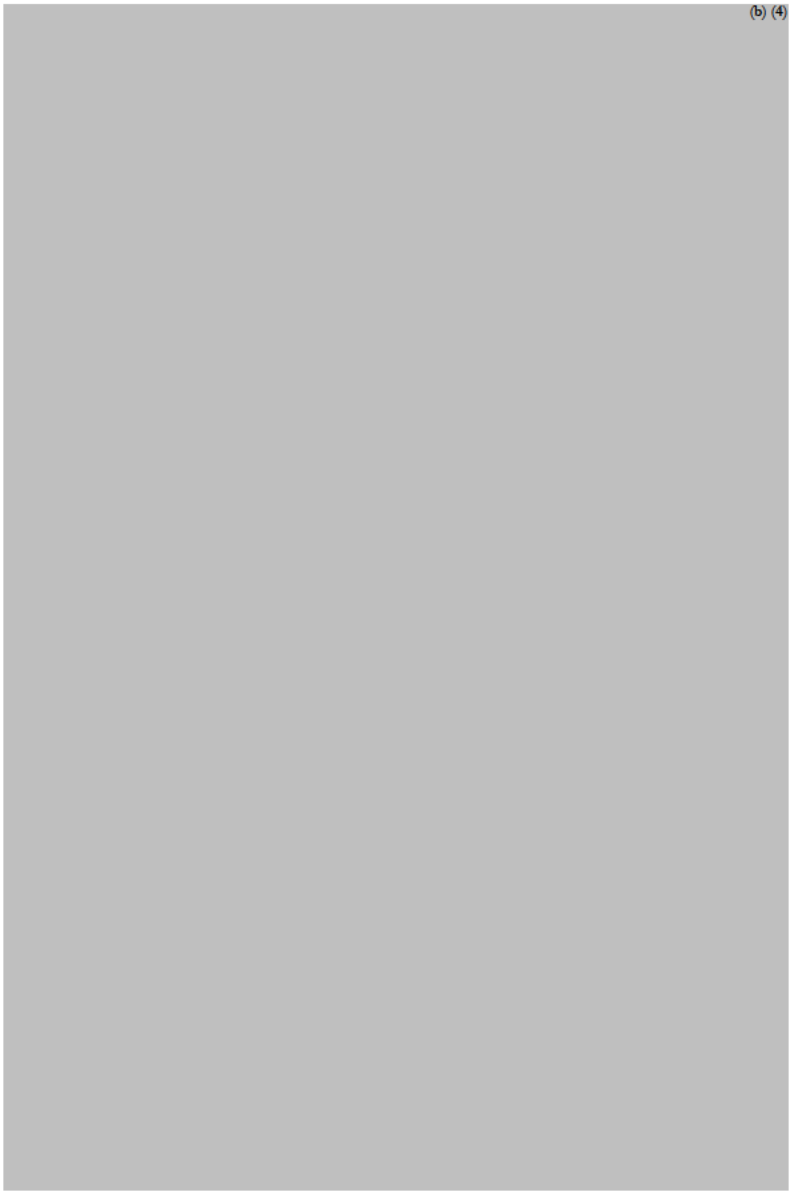


Figure 5

Pharmacokinetic exposure parameter of Nefazodone (NEF) and its primary metabolites between depressed pediatric patients (children vs. adolescents). The results were contrasted to those from healthy adults (study CN104068). (b) (4)

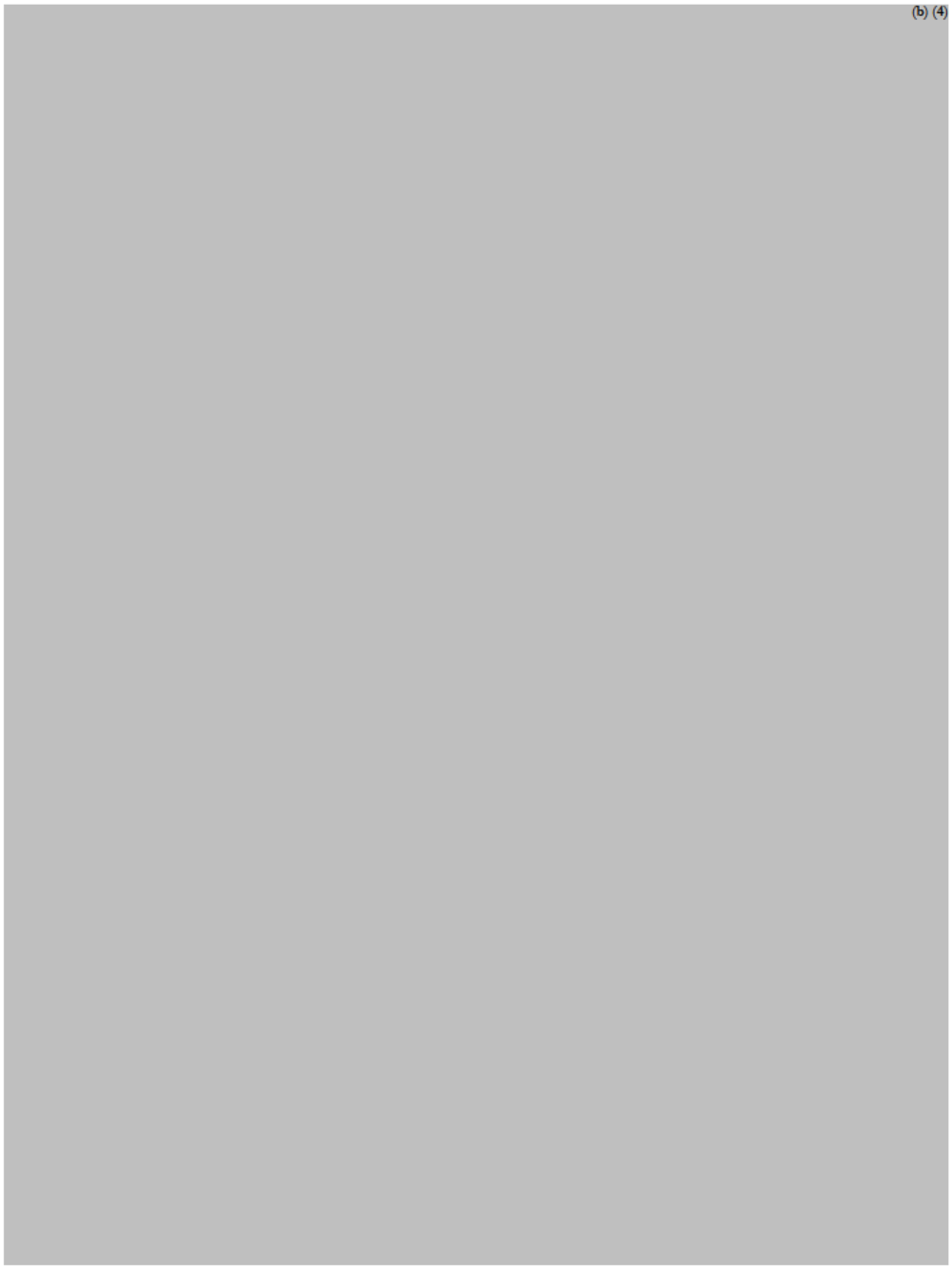
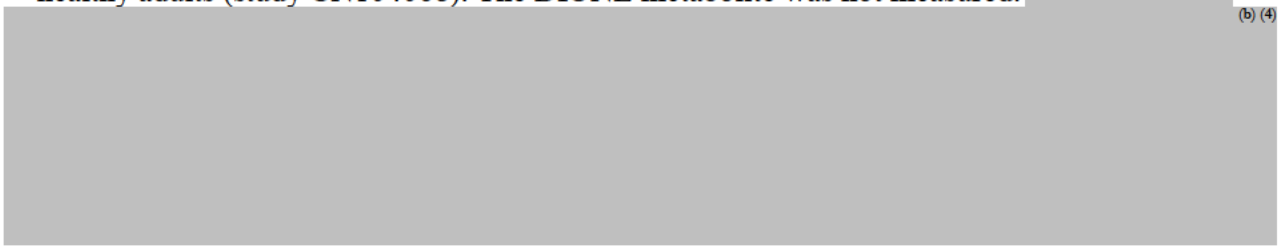
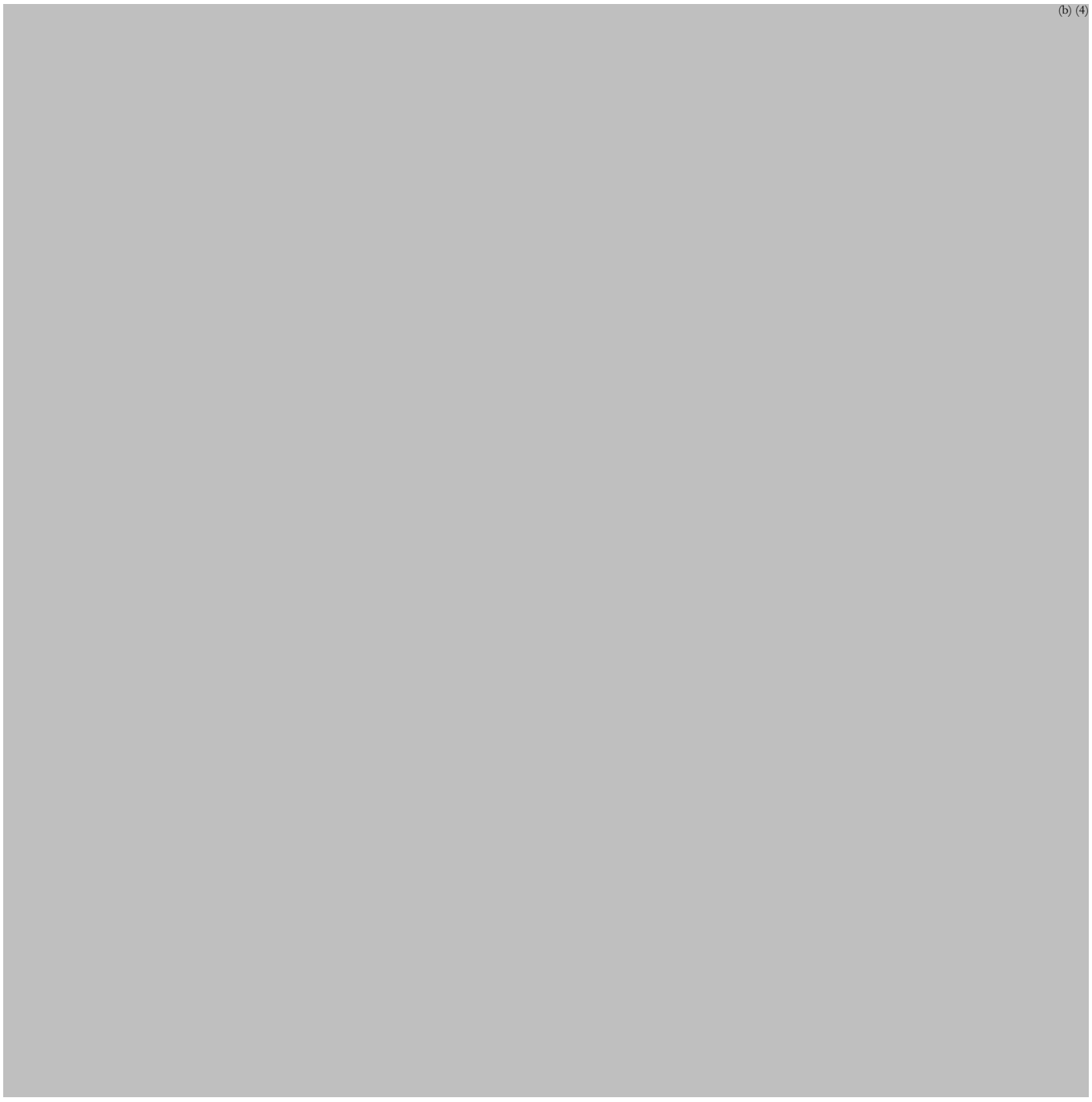


Figure 6

Comparative exposure measures of Nefazodone (NEF) and its primary metabolites between depressed pediatric patients (children vs. adolescents). The results were contrasted to those from healthy adults (study CN104068). The DIONE metabolite was not measured. (b) (4)




(b) (4)


(b) (4)

Data from CN104136 (children and adolescents) and CN104068 (adults) were combined to evaluate the relationship between the pharmacokinetic parameters AUC(TAU) and Cmax of nefazodone, hydroxy-nefazodone, mCPP, and DIONE and body weight (kg). Age was excluded from this analysis since the oldest subject in CN104136 was 16 years old and the youngest subject in CN104068 was 40 years old. There were 13 children, 13 adolescents, and 12 adults in the combined data set. The results are shown in Table 7.

Reviewer's comment:

The study was titled 'An open-label pharmacokinetic trial of nefazodone in depressed children and adolescents.'

1. Nefazodone at 100-mg BID, is a low dose and does not match the actual dose given later during this trial. With respect to the nonlinear behavior of nefazodone and its metabolite OH-NEF it is difficult to extrapolate from these results to higher standard NEF doses.

2. Conclusion: This pharmacokinetic study regarding the effects of nefazodone and its metabolites showed that there is a trend that children have (b) (4) of NEF and its metabolites than adults and adolescents. Adolescents in turn may be (b) (4) to adults.

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/s/

Carl-Michael Staschen
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PHARMACOLOGIST

Raman Baweja
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BIOPHARMACEUTICS