CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Paxil ® (Paroxetine)
NDA: 20-031 SE5-037
FORMULATION: Tablet
APPLICANT: Glaxo SmithKline

PRIMARY REVIEWER: Andre Jackson
TYPE: Pediatric supplement (7-17 years)
STRENGTH: 10, 20, 30 mg
SUBMISSION DATES: 4-11-02
7-3-02
8-8-02

INDICATION: Obsessive Compulsive Disorder(OCD) or Depression
Generic Name: Paroxetine

1.EXECUTIVE SUMMARY

The sponsor has conducted two clinical studies (one each in OCD and depressed pediatric patients). A pharmacokinetic study was done with Paxil in 62 pediatric depressed or OCD patients (27 children and 35 adolescents) aged 7-11 years and 12-17 years respectively (Study no. 715). Paxil is metabolized by CYP2D6 and has phenotypically extensive metabolizers (EM) and poor metabolizers (PM) within the population. The current study population was found to consist mainly of EM subjects. The study was conducted as a dose-rising study involving 10 mg/day, 20 mg/day and 30 mg/day dosing for 14 days with steady-state samples taken on day 14 from 0-24 hrs for each dose.

This Clinical Pharmacology/Biopharmaceutics review will evaluate whether the applicant has adequately described the pharmacokinetics of Paxil in the pediatric population (b) (4)

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1.1 Recommendation: The pharmacokinetic studies provided in this pediatric supplement for Paxil submitted to the Division of Neuropharmacological Drug Products to fulfil the pediatric written request provide an understanding of the pharmacokinetics of Paxil in pediatric patients between the ages of 7 and 17 years, inclusive. This submission is acceptable from the OCPB perspective.

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2. Introduction and Background:

BRL 29060 (paroxetine hydrochloride; Paxil®) is an orally administered selective serotonin reuptake inhibitor (SSRI) used in the treatment of OCD and depression, conditions which occur not only in adults, but also in the pediatric population. The pharmacokinetic profile of paroxetine has been fully characterized in the adult population. In single dose studies, paroxetine plasma concentrations increase disproportionately with dose in most subjects, but not in all. In PM subjects (poor metabolizers who lack CYP2D6), concentrations are the highest initially but increase linearly with dose. Similarly, in repeat dose studies, although most subjects show greater than predicted paroxetine accumulation during the approach to steady state, accumulation in PMs is entirely predictable; non-linearity is confined to EMs (extensive metabolizers). Importantly, although disproportionality is also evident when increasing the daily dose at steady state, the deviations from linearity are less pronounced because CYP2D6 is already partially saturated. In all of these dosing scenarios (increasing dose level and duration), the between-subject pharmacokinetic variability progressively diminishes. These properties indicate that all subjects (EMs and PMs) have alternative, non-saturable pathways by which paroxetine is cleared from the body when CYP2D6 is absent or saturated. These linear pathways predominate at steady state, and therefore the influence of CYP2D6 status as a determinant of pharmacokinetic properties during the routine clinical use of paroxetine is much reduced. Also, because paroxetine plasma concentrations are not predictive of clinical outcome (efficacy or AEs) , the same starting doses and titration regimens are suitable for EMs and PMs alike.

In the pediatric population, the pharmacokinetic profile of paroxetine has only previously been described across a limited range of doses. Thirty depressed pediatric patients (6-17 years) each received a single 10 mg dose, followed by repeated once daily dosing at 10 mg, with an optional increase to 20 mg after 4 weeks. The single dose half-life (average 11.1 hours) was reported to be shorter than in adults, possibly suggesting higher paroxetine clearance, but other pharmacokinetic features mirrored the adult population. In particular, when the daily dose was doubled from 10 to 20 mg, average paroxetine steady state plasma concentrations increased nearly seven-fold. Moreover, the broad between-subject variability in clearance was related to CYP2D6 activity. Finally, once steady state had been achieved (usually within a week), no further pharmacokinetic changes were evident in these pediatric patients.

Because information on the disposition of paroxetine at therapeutic doses in the pediatric population is lacking, a study was designed to descriptively assess the steady state pharmacokinetics of paroxetine in children and adolescents receiving sequentially ascending doses of 10, 20 and 30 mg once daily for successive two-week periods. These doses were chosen because they are the starting dose and the first two permitted dosage increments which were investigated in concurrent clinical trials in pediatric patients with depression or OCD.

3.CURRENT SUBMISSION- This report contains results from an in-vivo steady-state pharmacokinetic study (#715) at 10 mg/day, 20 mg/day and 30 mg/day in children and adolescents with depression or obsessive compulsive disorder(OCD). Approximately 30 children ages seven to 11 years, inclusive, and approximately 30 adolescents ages 12 to 17 years, inclusive, who currently met DSM-IV criteria for OCD and/or depression (MDD)

were enrolled in this study. Each age group was enrolled such that a ratio no greater than 2:1 was achieved based upon gender.

4. CLINICAL PHARMACOLOGY QUESTION BASED REVIEW

4.1 General Attributes

Pharmacodynamics

The efficacy of paroxetine in the treatment of major depressive disorder, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD), generalized anxiety disorder (GAD) and posttraumatic stress disorder (PTSD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics:

Paroxetine is equally bioavailable from the oral suspension and tablet.

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n=15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of Cmax, Tmax, Cmin and T1/2 were 61.7 ng/mL (CV 45%), 5.2 hr. (CV 10%), 30.7 ng/mL (CV 67%) and 21.0 hr. (CV 32%), respectively. The steady-state Cmax and Cmin values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC0-24 was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.
In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to Cmin values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the Cmax was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome P4502D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions.

Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Distribution: Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Protein Binding: Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

4.2 What were the bioanalytical methods used to assess concentration?

An on-line solid-phase, automated PROSPEKT® extraction procedure was used to isolate the analyte from 0.1-mL aliquots of human plasma. Samples extracts were analyzed by turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS) in the positive ion mode. The lower limit of quantitation was 0.1 ng/mL for paroxetine. The calibration curves for paroxetine were linear from 0.1 ng/mL to 50 ng/mL. The coefficients of determination of the calibration curves were 0.9935.

Was the method properly validated?

The bioanalytical method used for paroxetine analysis of the plasma samples from the in vivo study in NDA 20-031 is considered adequately documented and validated although it appeared that for several subjects there were assay problems at the LOQ although this was not explicitly stated by the firm. The reason for most sample repeats was that the sample required dilution for analysis within the calibration curve range.

4.3 IN VIVO STUDIES

4.3.1 Has the sponsor adequately evaluated the pharmacokinetics of Paxil in the pediatric population?

The sponsor conducted a multicenter, open-label, repeat dose, dose-rising study in children and adolescents with OCD and/or depression. Each patient received paroxetine hydrochloride orally according to the following schedule:

Days 1-14	10 mg once daily
Days 15-28	20 mg once daily
Days 29-42	30 mg once daily
Days 43-49	Dose-tapering (20 mg once daily)
Days 50-56	Dose tapering (10 mg once daily)

The study was done in 25 children ages 7 to 11 years, inclusive, and 34 adolescents ages 12 to 17 years, inclusive, who currently met DSM-IV criteria for OCD and/or depression (MDD) were enrolled in this study. Each age group was to be enrolled such that a ratio no greater than 2:1 was achieved based upon gender if possible.

The safety and tolerability of protocol-specified treatments were assessed by vital signs, 12-lead ECGs, clinical laboratory tests and clinical monitoring.

Pharmacokinetic Parameters

Serial blood samples were collected over a 24 hour dosing interval after the final dose at each dose level. Plasma concentrations of paroxetine were quantitated using a method based on LC/MS/MS with on-line solid-phase extraction. Paroxetine Cmax, Tmax, AUC(0-24), CL/F and C(24) were derived using non-compartmental pharmacokinetic analysis, and their relationships with dose, age, weight, gender and CYP2D6 genotype were explored.

During the data analysis the firm had problems with assay sensitivity and for many of the Time=0 or Time =24 hour samples they substituted either a value=1/2LLQ or Time 0 for 24 hour (i.e., if 24 hr not quantifiable) or Time 24 for Time 0 (i.e., if 0 hr not quantifiable). There were 3 children (10% of the population) and 9 adolescents(26% of the population) that exhibited these problems with their data. This was addressed by fitting the steady-state data to a 1 compartment oral absorption model (2 compartment model objective function value-9223; 1 compartment model-7091) using NONMEM in order to obtain fitted predictions for these missing values or non quantifiable values. Based upon the FDA analysis of the data of the subjects in question, the following ratios for FDA area /Firm's area were obtained.

Table 1. Pediatric subjects with time=0 or time=24 analysis problems. The AUC(0-24) values for the FDA were obtained by replacing the values in question by the best fit value from the NONMEM analysis.

Dose	#	Type	FIRM COMMENTS	FDA AREA/FIRM AREA
10 mg	055	CHILD	T=0 NQ given value=1/2 LLQ	1.00
10 MG	101	CHILD	All values <LLQ	--

10 MG	604	CHILD	T=0 NQ given value=1/2 LLQ	1.01
10 MG	004	ADOL	T=0 NQ given value=1/2 LLQ	1.00
10 MG	052	ADOL	T=24 given value at T=0	1.21
10 MG	109	ADOL	T=0 T=1 NQ given value=1/2 LLQ	1.07
20 MG	109	ADOL	T=0 NQ given value=1/2 LLQ	1.03
30 MG	109	ADOL	T=0 NQ given value=1/2 LLQ	1.13
10 MG	502	ADOL	T=24 NQ given value at T=0	1.00
30 MG	502	ADOL	T=24 NQ given value at T=0	1.10
10 MG	503	ADOL	T=0 T=1 NQ given value=1/2 LLQ	1.05
20 MG	804	ADOL	T=0 NQ given value at T=24	0.99

The ratio of the FDA area /Firm area was nearly 1 except in 3 cases therefore it would appear that the data was not biased by the firm setting time=0 and or time =24 values equal to ½ LOQ or by substituting the Time 0 for 24 hour (i.e., if 24 hr not quantifiable) or Time 24 for Time 0 (i.e., if 0 hr not quantifiable).

The firm also excluded parameter values (e.g., AUC0-24 that appeared to be high or low compared to other values) in their analysis stating that it was suspect and giving reasons as internal data inconsistencies . These values are listed in Tables 10.3-10.14 (pages 413-425) in the April 11, 2002 submission.

The firm's rationale for deleting these subjects were as follows:

Patient 101 (Child; Table C.4): Whereas low (but measurable) concentrations were recorded at 10 mg, concentrations at 20 mg remained below the LLQ throughout the 24 hour dosing interval. Concentrations at 30 mg were readily measurable, but the pre-dose value was more than three-fold lower than the corresponding value measured 24 hours later. Although compliance in this child was reportedly good, these irregularities were considered to render the entire data-set unreliable.

Patient 110 (Child; Table C.10): At 10 mg, the pre-dose concentration was four-fold lower than the corresponding value measured 24 hours later, probably because no dose was taken on the previous day. In addition, at 30 mg, several doses were missed during the previous week. Since the plasma concentration versus time curves at these dose levels could not be considered to represent a true steady state, both were deemed unevaluable.

Patient 109 (Adolescent; Table C.36): At all three dose levels, concentrations were below the LLQ pre-dose (and for up to 2 hours post-dose). However, at 24 hours post-dose, concentrations were readily measurable and, by inference, at least 5- to 50-fold higher than the pre-dose values. Since compliance in this adolescent patient was found to be unreliable, the entire data-set was discounted.

Patient 602 (Adolescent; Table C.47): The first 30 mg dose was inadvertently administered on the day scheduled for pharmacokinetic sampling at 20 mg.

Therefore, the concentrations measured on this day are uninterpretable.

Based upon the firm's explanations, the FDA concluded the following:

1.For child 101 all data should be retained since the problems may be assay related
2.Child 110, only drop the 30 mg dose since this was the only dose impacted by dosing errors
3.All adolescent patient 109 data should be dropped due to low compliance
4.For adolescent 602 the 20 mg dose should be dropped due to the dosing error

All other parameter values submitted by the firm **were retained for all FDA statistical analysis.**

Table 2. Comparison of steady-state Cmax, AUC(0-24) and CL/F values for children and adolescents. Values calculated by the FDA.

Paroxetine steady state			**Children**		**Adolescents**		
Pharmacokinetic parameter		**10 mg**	**20 mg**	**30 mg**	**10 mg**	**20 mg**	**30 mg**
[units]		[n=25]	[n=23]	[n=22]	[n=33]	[n=29]	[n=27]
Cmax	Mean	18.2	58.6	125.9	12.0	42.7	94.0
[ng/mL]	SD	17.9	34.5	105.3	13.0	30.0	51.4
	Minimum	0.3	19.4	28.3	0.3	10.7	28.5
	Maximum	90.9	142.4	552.6	62.8	129.9	262.9
	Geom. Mean	**11.5**	**50.0**	**102.9**	**6.5**	**34.8**	**82.3**
AUC(0-24)	Mean	265.6	899	2027.5	189.4	732.9	1631.4
ng.h/mL]	SD	289.0	552	1713.5	227	581	1039.6
	Minimum	3.5	295	529	3.85	149.5	501.4
	Maximum	1424	2633	9018	1134	2628	5485
	Geom. Mean	**156**	**772**	**1660.7**	**93.7**	**566.8**	**1394.1**
CL/F	Mean	203.2	29.8	21.2	273.3	44.4	24.8
[L/h]	SD	563.3	15.9	12.3	495.8	32.3	13.2
	Minimum	7.0	7.6	3.3	8.8	7.6	5.5
	Maximum	2824.8	67.9	56.7	2597.4	133.8	59.8
	Geom. mean	**64.2**	**25.9**	**18.0**	**105.6**	**34.8**	**5.4**
CL/F	Mean	4.96	0.73	0.51	3.63	0.64	0.36
(weight-	SD	13.88	0.37	0.33	5.79	0.37	0.16
Normalized)	Minimum	0.26	0.20	0.12	0.16	0.09	0.12
[(L/h)/kg]	Maximum	69.41	1.76	1.47	29.58	1.52	0.78
	Geom. mean	**1.60**	**0.64**	**0.43**	**1.63**	**0.53**	**0.32**

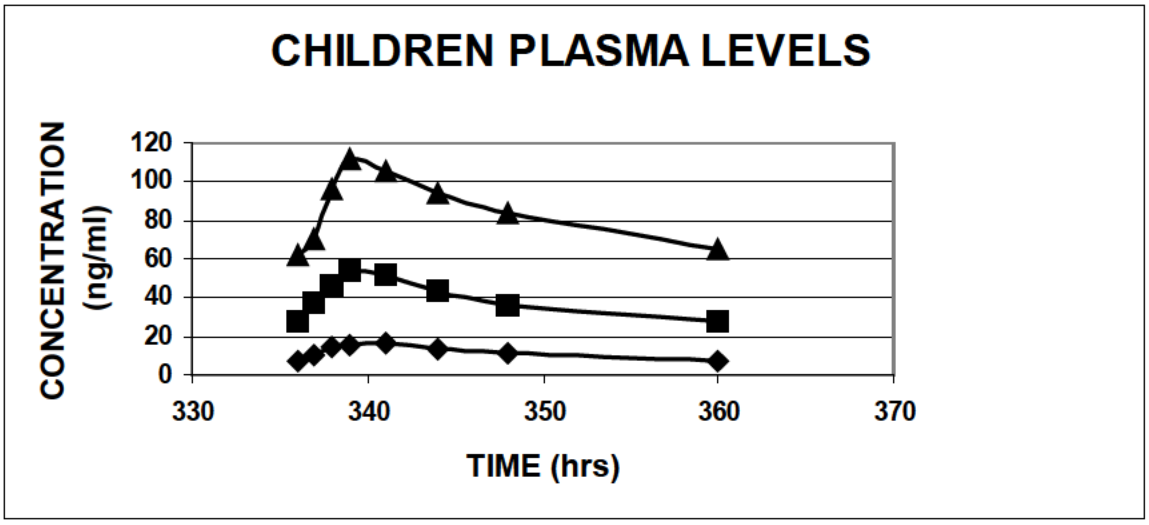

Figure 1. Children mean paxil plasma levels following doses of 30 mg/day(▲), 20 mg/day(■) and 10 mg/day(♦) on the last day of dosing.

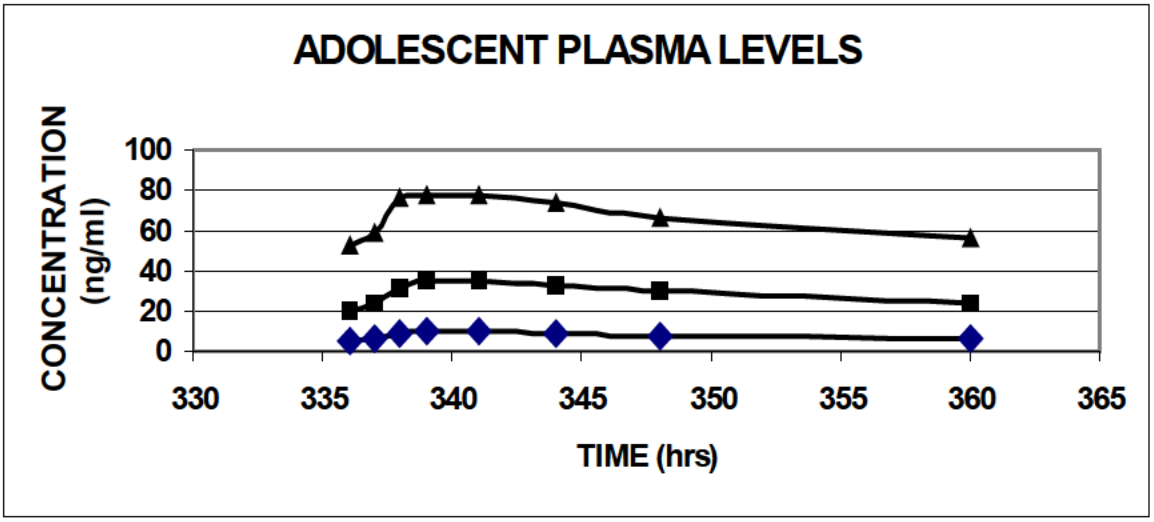

Figure 2. Adolescent mean paxil plasma levels following doses of 30 mg/day(▲), 20 mg/day(■) and 10 mg/day(♦) on the last day of dosing.

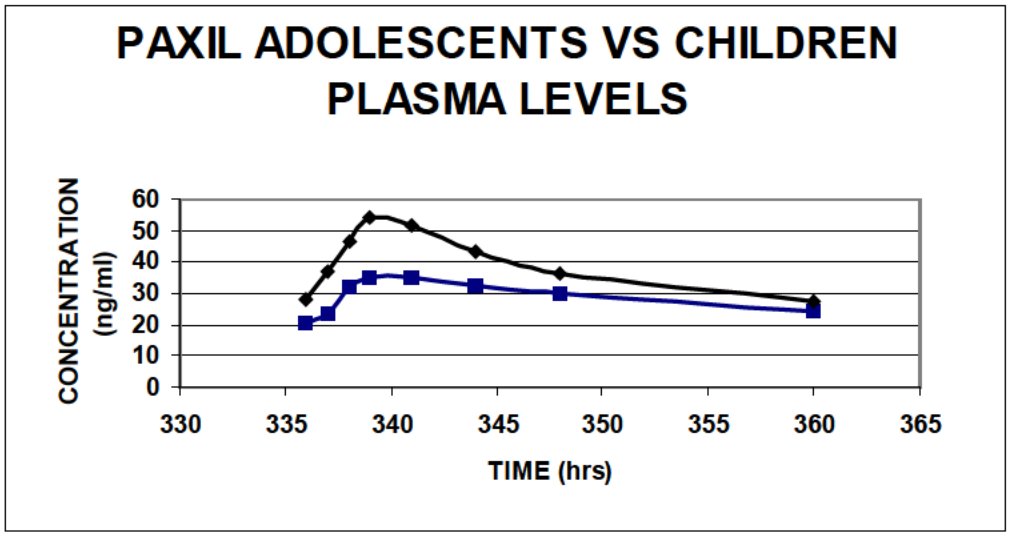

Figure 3. Comparative steady-state Paxil plasma levels following the final dose on day 14 for all adolescents (■) vs all children (♦)following the 20 mg/day regimen.

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4.4. *Are there any intrinsic factors which impact the kinetics in children or adolescents* (b) (4) *?*

4.4.1 Gender Effects:

Table 5. Comparison of steady-state parameters for male versus female children and adolescents. N=(6-7) female children; N=(16-18) male children; N=(13-14) female adolescents; N=(15-20) male adolescents

	CHILD M		CHILD F		ADOL M		ADOL F	
Variable	Mean	Std	Mean	Std	Mean	Std	Mean	Std
AUC10 ng/mlxhr	304.4	320.34	165.97	150.26	174.94	252.03	211.83	189.75
AUC20 ng/mlxhr	872.57	586.76	975.24	478.22	664.7	566.75	816.75	610.77
AUC30 ng/mlxhr	2130.5	2027.61	1806.68	774.86	1577.82	1190.16	1698.43	862.06
CMAX10 ng/mlxhr	20.76	19.99	11.6	9.63	10.67	13.88	14.05	11.66
CMAX20 ng/mlxhr	57.94	35.54	60.55	34.6	39.23	27.88	47.07	33.01
CMAX30 ng/mlxhr	137.18	123.72	101.9	46.29	94.81	60.02	93.05	40.67
CL10/F L/hr	96.37	160.01	477.85	1036.64	233.36	301.99	334.75	710.18
CL20/F L/hr	31.21	16.75	25.81	13.83	44.3	28.16	44.53	38.07
CL30/F	21.48	13.25	20.5	11.17	25.87	13.55	23.4	13.29

L/hr								
CLWT10/F (L/hr)/kg	2.51	4.13	11.29	25.64	3.26	3.94	4.2	8.02
CLWT20/F (L/hr)/kg	0.81	0.39	0.49	0.2	0.66	0.34	0.63	0.43
CLWT30/F (L/hr)/kg	0.56	0.37	0.42	0.22	0.37	0.14	0.36	0.2

SAS analysis of the children and adolescent data based upon gender and age indicated 2 parameters with significant differences. Comparisons which reached a level of significance at the p=0.05 level are presented in Table 6.

Table 6. Steady-state children versus adolescent and gender parameters that were statistically significant at p=0.05.

PARAMETER	MEAN	STDV	MEAN	STDV	P
CL20/F	29.8 ALL CHILDREN	15.92	44.4 ALL ADOLESCENTS*	32.3	0.014
CLWT20/F	0.49-F CHILD	0.20	0.81-M CHILD	0.39	0.036

4.4.2 DOSE, WT, IDEAL BODY WEIGHT, AGE GENDER AS COVARIATES

The following intrinsic factors were investigated (i.e., dose, wt, ideal body weight, age, gender) on AUC, Cmax and CL/F. Ideal body weight was defined according to gender as:

Males=2.3*(HT-60)+50;
Females=2.3*(HT-60)+45.5;

Multiple linear regressions were done for the children (including adolescents) data (b) (4)

Significant regressions were as follows:

Children:

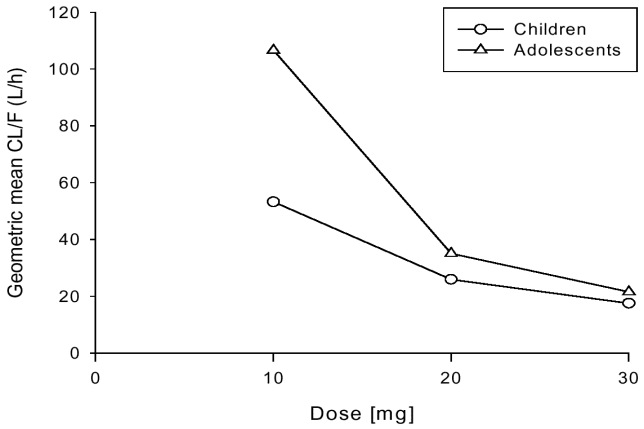
Cmax=4.7*Dose – 0.616*Wt
AUC = 76.17*Dose – 9.85*Wt
CL = -11.25*Dose + 1.22*IBW

(b) (4)

4.4.3 Phenotype

The reason for the decrease in Cmax and AUC with dose is the apparent non linear bioavailabilty due to the metabolism by CYP2D6 as represented in Figure. 1.

Figure 1: Relationship between paroxetine oral clearance and daily dose in pediatric patients



The phenotype presented in the following tables indicate that almost all subjects were extensive metabolizers. Results are presented in Tables 7 and 8.

Table 7 CYP2D6 phenotype in child patients predicted from genotype analysis

Patient	Functional alleles	Predicted Phenotype
001	1	EM
053	2	EM
055	2	EM
101	ND	ND
102	2	EM
104	1	EM
106	ND	ND
107	2	EM
108	2	EM
110	1	EM
112	1	EM
202	ND	ND
301	2	EM
303	2	EM
504	2	EM
603	1	EM

604	1	EM
702	1	EM
704	1	EM
705	1	EM
707	ND	ND
708	2	EM
709	2	EM
806	2	EM
818	1	EM

ND = not determined

Table 8. CYP2D6 phenotype in adolescent patients predicted from Genotype analysis

Patient	Functional alleles	Predicted phenotype
002	2	EM
003	2	EM
004	1	EM
005	2	EM
007	1	EM
051	0	PM
052	2	EM
054	2	EM
103	0	PM
105	2	EM
109	2	EM
201	ND	ND
401	ND	ND
502	2	EM
503	2	EM
505	2	EM
506	1	EM
507	2	EM
509	2	EM
510	0	PM
601	2	EM
602	2	EM
605	2	EM
606	2	EM
607	1	EM
701	2	EM
706	2	EM
804	2	EM
805	2	EM
809	2	EM
811	2	EM
816	2	EM
824	2	EM

825 1 EM

ND = not determined

4.5. (b) (4)

(b) (4)

4.6. Is there a discernable PK/PD relationship with efficacy or toxicity endpoints?

There was no PD data related to efficacy. Toxicity data, QRT interval summary data was presented and summarized by the firm as follows:

The firm reported no QT or QTc values above 500 msec were observed during this study. However, four patients (two children – Patients 00603 and 00708 and two adolescents – Patients 00502 and 00805), representing 6.5% of the total study population, had post-dose QTc increases greater than 30 msec relative to screen. Three (3) of these patients were female (Patients 00708, 00502 and 00805) and one (1) was male (Patient 00603). The largest such increase was 42 msec in a female adolescent (Patient 00805). None of these patients had exposure (measured by AUC) near the upper range for the patients enrolled in their age group. In each case, the ECG was not considered to have clinically significant abnormalities by the investigator. The FDA has requested raw QTc interval data in children and adults since this parameter has not been investigated in the past by the medical staff in the Division of Neuropharmacological Drug products.

The sponsor notified the FDA via E-mail on September 16, 2002 that it will take several months to complete the QT data collation. Therefore, the issue remains an open item since the firm has made the commitment to supply the data to the FDA.

4.7. (b) (4)

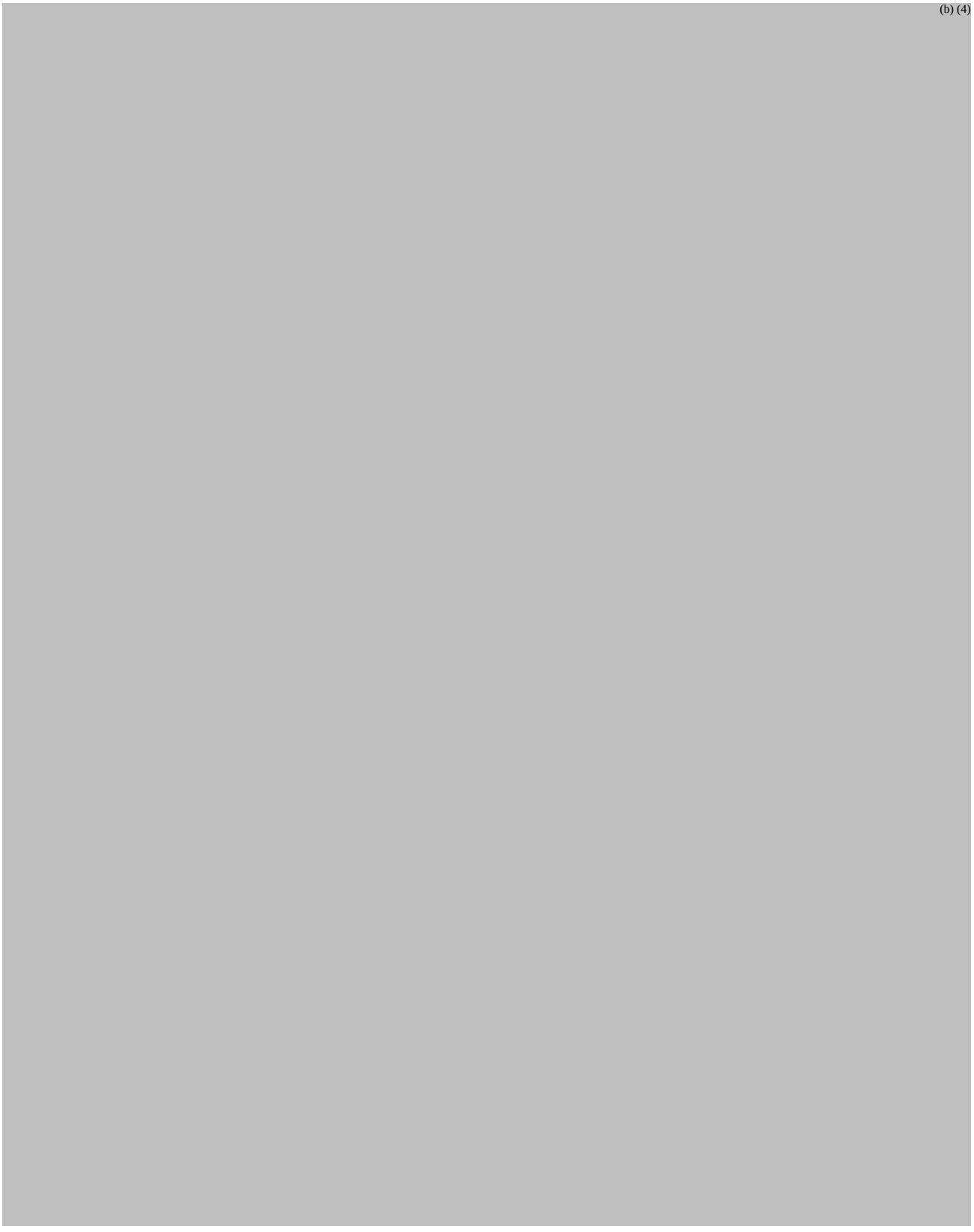
(b) (4)

4.7.Conclusions:

Paroxetine steady state Cmax, AUC(0-24) and CL/F (before and after normalization for body weight) indicate a non-linear increase in AUC and Cmax between the 10 mg, 20 mg and 30 mg/24 hour doses. For a 2 fold increase in dose between 20 and 10 mg/day the increase in AUC and Cmax were between 3-6. There did appear to be a decrease in intersubject variabilty with increase in dose. The phenotype for the

subjects in the study were extensive metabolizers which is consistent with the pattern observed for AUC and Cmax.. The non-linear effects decrease after 10 mg dose since the CYP2D6 is partially saturated and the linear pathway dominates.

(b) (4)



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RD/FT initialized by Ray Baweja, Ph.D._____

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Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Date: September 24, 2002(Laughren,Mosholder, Sahajwalla,Jackson,Baweja)

cc: NDA 20-031 SE5-037,HFD-120(Mosholder,/CSO/P. David), HFD-860(Mehta, Baweja, Jackson)

APPENDIX

7.1 Individual Study Report

Study 29060/715

Objective: This study was designed to evaluate the pharmacokinetics of paroxetine in pediatric patients following multiple doses of 10mg/day, 20 mg/day and 30 mg/day.

Study Design:
Each patient was scheduled to receive paroxetine once daily for six weeks, beginning at 10 mg/day for the first two weeks, increasing to 20 mg/day for the next two weeks and finally 30 mg/day for the last two weeks. Some flexibility was permitted in the dosing periods but, to ensure that steady state conditions had been established, pharmacokinetic measurements were only made after at least 11 days of dosing at each dose level.

Pharmacokinetic Sample Collection:

Serial blood samples were collected over a 24 hour dosing interval after the 15th dose at 0, 1,2,3,4,5,6,7,8,9,10,12,14,16,18 and 24 hrs, for each dose level.

Bioanalytical Procedure:

The same analytical method was used to generate all the paroxetine pediatric pharmacokinetic data in this submission:

Quantitation of BRL-29060 in human plasma was done by turbo ion-spray LC/MS/MS. This method was validated and implemented (b) (4) based on a method originally developed in the Department of Drug Metabolism and Pharmacokinetics, SmithKline Beecham, King of Prussia, PA.
The method involves on-line solid-phase extraction followed by LC/MS/MS, with detection and quantitation of paroxetine by means of positive-ion turbo ion-spray ionization. The lower limit of quantitation is 0.1 ng/mL and the validated range is 0.1 to 50.0 ng/mL, based on a 0.1 mL plasma aliquot (smaller aliquots are used when measuring higher concentrations). Results for 28 runs are presented in the following table.

Table 1. Precision for Paxil calibration samples

Calibrator Concentration	Precision %CV	% Accuracy
0.1 ng/ml	6.3	99.8
0.2 ng/ml	5.3	101.7
0.5 ng/ml	5.5	99.8
1.0 ng/ml	5.2	102.7
2.0 ng/ml	3.6	102.0
5.0 ng/ml	3.9	99.7

10 ng/ml	4.3	102.5
20 ng/ml	4.1	101.0
30 ng/ml	4.6	98.9
40 ng/ml	4.6	98.3
50 ng/ml	4.3	98.4

Table 2. Precision and accuracy for Paxil control samples

Calibrator Concentration	Precision %CV	% Accuracy
0.1 ng/ml	6.5	101.9
20 ng/ml	6.9	99.9
40 ng/ml	6.4	99.5

Most samples were re-assayed due to the original value exceeding the upper limit of the calibration curve. These samples required dilution prior to analysis.

Table 3. Stability sample data for Paxil

Stability	
Room temperature	24 hr
Mobile phase	24 hr
Control samples (-20 ^{0} C)	9 months
Authentic human samples (-20 ^{0} C)	9 months
Freeze-thaw (-20 ^{0} C)	3 cycles

Overall the assay was acceptable.

Statistical Analysis:

Paroxetine data were subjected to non-compartmental pharmacokinetic analysis. Steady state Cmax, Tmax, C(24), AUC(0-24) and oral clearance (CL/F) both before and after normalization for body weight were summarized using descriptive statistics. Relationships with dose, age, weight, gender and CYP2D6 genotype were explored.

Patient Demographics:

Table 4. Patient demographics for the subjects in study 29060/715

		Age (years)	Height (cm)	Weight (kg)
Children	**Mean**	10	142.9	42.1
N = 27	**SD**	1.1	9.63	13.62
74% Male, 26% Female	**Range**	7-11	125.5-164.0	25.9-76.5
Adolescents	**Mean**	14	164.5	68.2
N = 35	**SD**	1.8	12.41	22.96

57% Male, 43% Female	**Range**	12-17	129.0-190.5	30.1-141.0
Pooled	**Mean**	12	155.1	56.8
N = 62	**SD**	2.8	15.53	23.31
65% Male, 35% Female	**Range**	8-17	125.5-190.5	25.9-141.0

Children: 85% White; 7% Black; 7% Other; **Adolescents**: 83% White; 11% Black; 6% Other; **Pooled**: 84% White; 10% Black; 6% Other

Pharmacokinetic Results:.

The mean plasma concentration curves for paroxetine in children and adolescents is presented in Figure 1.

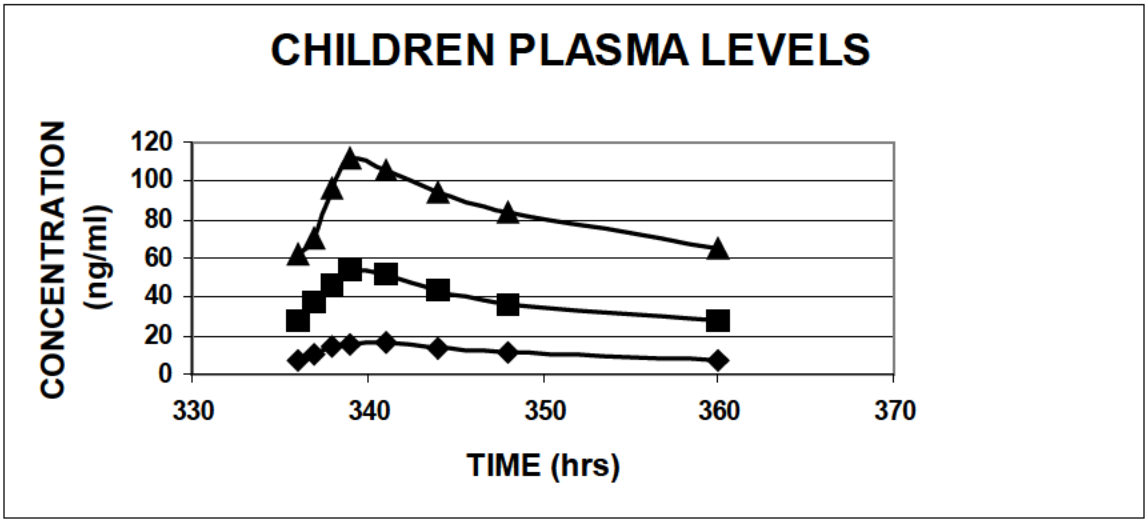

Figure 1. Children mean paxil plasma levels on the last day of dosing following doses of 30 mg/day(▲), 20 mg/day(■) and 10 mg/day(♦).

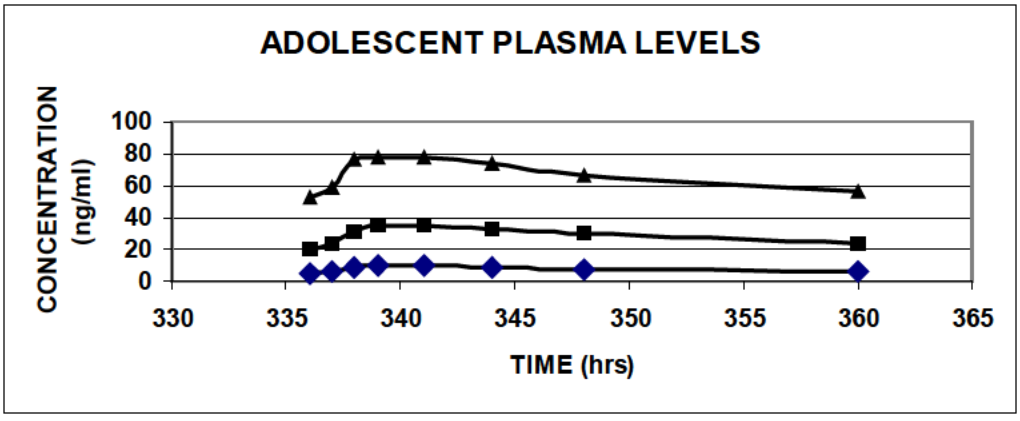

Figure 2. Adolescent mean paxil plasma levels on the last day of dosing following doses of 30 mg/day(▲), 20 mg/day(■) and 10 mg/day(♦).

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OCPB FILING FORM

Office of Clinical Pharmacology and Biopharmaceutics						
	New Drug Application Filing and Review Form					
	General Information About the Submission					
		Information				Information
NDA Number	**20-031 (SE 5-037)**		**Brand Name**		**Paxil**	
OCPB Division (I, II, III)	**I**		**Generic Name**		**Paroxetine HCL**	
Medical Division	**Neuropharmacological**		**Drug Class**		**antidepressant**	
	(HFD-120)					
OCPB Reviewer	**Andre Jackson**		**Indication(s)**		**Major depressive disorder**	
					and obsessive	
					compulsive disorder	
OCPB Team Leader	**Raman K.Baweja**		**Dosage Form**		**Tablets; oral solution**	
			(b) (4)			
Date of Submission	**4/11/02**		**Route of Administration**		**p.o.**	
Estimated Due Date of OCPB Review	**End of August**		**Sponsor**		**GlaxoSmithKline**	
PDUFA Due Date	**10/11/02**		**Priority Classification**		**P**	
Division Due Date	**9/11/02**					
	Clin. Pharm. and Biopharm. Information					
This pediatric supplement is a response to a Written Request from FDA. Children and adolescents aged 7 to 17 years were studied						
in a traditional PK design in 62 subjects (actual age group recruited is 8 to 17 years). Forty males and 22 females were enrolled.						
Trough samples were also obtained in some pivotal clinical trials. (b) (4)						
	"X" if included		**Number of**	**Number of**	**Critical Comments If any**	
		at filing	**studies**	**studies**		
			submitted	**reviewed**		
STUDY TYPE						
Table of Contents present and		**X**				
sufficient to locate reports, tables, data,						
etc.						
Tabular Listing of All Human Studies		**X**				
HPK Summary		**X**				
Labeling		**X**				
Reference Bioanalytical and Analytical		**X**			**Summary provided.**	
Methods						
I. Clinical Pharmacology						
Mass balance:		**NA**				
Isozyme characterization:		**NA**				
Blood/plasma ratio:		**NA**				
Plasma protein binding:		**NA**				
Pharmacokinetics (e.g., Phase I) -						
Healthy Volunteers-						
	single dose:	**NA**				
	multiple dose:	**NA**				
Patients-						
	single dose:	**NA**				

	multiple dose:	**X**	**1**	1		
Dose proportionality -						
fasting / non-fasting single dose:		**NA**				
fasting / non-fasting multiple dose:		**X**	**1**	1		
Drug-drug interaction studies -						
In-vivo effects on primary drug:		**NA**				
In-vivo effects of primary drug:		**NA**				
	In-vitro:	**NA**				
Subpopulation studies -						
	ethnicity:	**NA**				
	gender:	**x**	**1**	1		
	pediatrics:	**x**	**1**	1		
	geriatrics:	**NA**				
renal impairment:		**NA**				
hepatic impairment:		**NA**				
PD:						
	Phase 2:	**NA**				
	Phase 3:	**NA**				

PK/PD:					
Phase 1 and/or 2, proof of concept:	**NA**				
Phase 3 clinical trial:	**NA**				
Population Analyses -					
Data rich:	**NA**				
Data sparse:	**NA**				
II. Biopharmaceutics					
Absolute bioavailability:					
Relative bioavailability -					
solution as reference:	**100%**		**NA**		
alternate formulation as reference:	**NA**				
Bioequivalence studies -					
traditional design; single / multi dose:	**X**				**Referred to previous NDAs**
replicate design; single / multi dose:	**X**				
Food-drug interaction studies:	**NA**				
Dissolution:					
(IVIVC):	**NA**				
Bio-wavier request based on BCS	**NA**				
BCS class	**NA**				
III. Other CPB Studies					
Genotype/phenotype studies:	**NA**				
Chronopharmacokinetics	**NA**				
Pediatric development plan	**x**		**1**	1	
Literature References	**X**		**5-6**		
Total Number of Studies			**7-8**		

	Filability and QBR comments				
	"X" if yes				**Comments**
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable)			
		(b) (4)			
Comments sent to firm ?		Please provide the following information electronically			
		1.	Provide dose, plasma concentration vs. time and demographic data (b) (4)		
		2.	Provide height and BSA measurements for pediatric (b) (4)		
			patients.		
		3.	Provide the analytical method validation report (BRL-29060/RSD-100z89/1)		
		4.	Provide genotyping data that was used to classify patients into PMs and EMs.		
		5.	(b) (4)		
		6. Please provide the plasma/serum concentration data obtained in studies 329, 676, 701 and 704 along with the patient demographics and analytical methodology.			
QBR questions (key issues to be considered)	**Are the pediatric pharmacokinetics adequately determined in this study?**				
	(b) (4)				
	Is there a discernable PK/PD relationship with efficacy or toxicity endpoints?				
	(b) (4)				
Other comments or information not ncluded above	**From the clinical Pharmacology point of view, the submitted information reasonably meets the terms of the written request (original 4/28/99 and amendment 2/28/00)**				
Primary reviewer Signature and Date					
Secondary reviewer Signature and Date					
CC: NDA 20-031, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-860 (C. Sahajwalla) HFD-120(P. David), HFD-860(R.Baweja, Jackson), CDR-Biopharm					

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

/s/

Andre Jackson
9/24/02 01:11:42 PM
BIOPHARMACEUTICS

Raman Baweja
9/24/02 01:38:03 PM
BIOPHARMACEUTICS