SUPPLEMENTAL NEW DRUG APPLICATION – PEDIATRIC INDICATIONS *CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW*			
NDAs:	20-151		20-699
SLRs:	024		030
Drug: **[Brand / Generic]**	Effexor Tablets (Venlafaxine HCl)		Effexor XR Extended Release Capsules (Venlafaxine HCl)
Sponsor:	Wyeth-Ayerst Philadelphia, PA	**Correspondence Date:**	September 25, 2002

1 EXECUTIVE SUMMARY

The sponsor has applied for approval of the indication of General Anxiety Disorder in pediatric patients (GAD). The sponsor also examined efficacy for Conduct Disorder with or without major depression and/or attention deficit disorder, and Major Depressive Disorder (MDD), however, these studies did not show any evidence of efficacy and the sponsor has not applied for approval of these indications in pediatric patients.

The efficacy studies for GAD were conducted with the ER formulation, whereas the initial pediatric pharmacokinetic studies were performed using the IR tablet formulation. Upon review of materials in a pre-NDA package OCPB requested a pediatric pharmacokinetic study with the ER formulation to assess if absorption of venlafaxine from an extended release formulation would be truncated before the end of the dosage interval. Collection of both of urine and feces was suggested to determine the fraction of the dose absorbed. In addition, since the youngest patients are most at risk for truncated absorption, and since the weight range in the protocols effectively excluded subjects less than 8 years old, the sponsor was requested to modify the weight range. In addition, and the sponsor was requested to study a minimum of 4 subjects in each of the following age brackets: 6-7 yo, 8-11 yo, and 12 – 17 yo.

Results of the pharmacokinetic studies suggest that exposure to venlafaxine is slightly lower in adolescents as compared to adults when dosed at the same mg/kg dose. Whereas when children are given the same mg/kg dose, exposures drop sharply as age declines in preadolescents. The data with the XR formulation suggests that preadolescent children may need on average a 2 to 4 fold higher mg/kg dose as compared to adults and that adolescents may need a 1.75 fold higher mg/kg dose. However, in the pivotal efficacy studies children received on average only a 1.33 fold higher dose on a mg/kg basis, and adolescents a 1.5 fold higher dose.

1.1 RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA 20-699 S-029 submitted September 25, 2002, and finds the sponsor's submission acceptable.

Comments and Labeling Comments should be communicated to the sponsor as appropriate.

1.2 COMMENTS TO THE SPONSOR:

Inspection of the pharmacokinetic data suggests that pediatric patients may have been under-dosed in the pivotal efficacy studies.

1.3 LABELING COMMENTS:

Since Effexor tablets will not be approved for use in the pediatric population, all descriptions of pediatric pharmacokinetic data should be removed from the tablet labeling.

For Effexor XR pharmacokinetic labeling has been edited to reflect OCPB's analysis of the data.

6 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page

2 SIGNATURES

_____ _____

Ronald E. Kavanagh, BS Pharm, Pharm.D., Ph.D., OCPB/DPE-1 **Date**

_____ _____

Raman Baweja, Ph.D., Team Leader, OCPB/DPE-1 **Date**

CC:

NDA	**20-151**	**(orig., 1 copy)**
	20-699	**(orig., 1 copy)**
HFD-120	**(MannheimG, AndreasonP, LaughrenT, KatzR, David)**	
HFD-860	**(BawejaR, KavanaghR, SahajwallaC, MehtaM)**	
CDR	**(B.Murphy)**	

Briefing

Level: Optional Intra-Division Briefing

Date: February 13, 2003

Time: 10:30 AM to 11:00 AM

Location: WOC2 RM2074

Attendees: BawejaR, KavanaghR, SahajwallaC, MehtaM

3 BACKGROUND

The present submission provides information to support pediatric exclusivity for venlafaxine.

The sponsor has applied for approval of the indication of General Anxiety Disorder in pediatric patients (GAD). The sponsor also examined efficacy for Conduct Disorder with or without major depression and/or attention deficit disorder, and Major Depressive Disorder (MDD), however, these studies did not show any evidence of efficacy and the sponsor has not applied for approval of these indications in pediatric patients.

The initial pediatric study was an efficacy study in conduct disorder using venlafaxine immediate release tablets that included a pharmacokinetic substudy. Although, the original pediatric exclusivity request dated April 28, 1999 was for MDD and GAD, the age range for MDD was subsequently modified in a revision to the written request on July 7, 2000.

On August 8, 2001, a meeting was held between the sponsor and the FDA to discuss the content and format of the anticipated supplemental NDA submission for GAD in pediatric patients, (the efficacy studies in MDD had not shown efficacy).

Upon review of the materials for this meeting, OCPB discovered that the pediatric pharmacokinetic study was conducted using the immediate release tablets whereas the efficacy studies had all been conducted using the extended release formulation. Due to the shorter GI transit times in pediatric patients an additional pediatric pharmacokinetic study was requested to assess if absorption of venlafaxine from an extended release formulation would be truncated before the end of the dosage interval. This would necessitate collection of urine and possibly feces, and measurement of all recovered metabolites. In addition, since the youngest patients are most at risk for truncated absorption, and since the weight range in the protocols effectively excluded subjects less than 8 years old, the sponsor was requested to modify the weight range. In addition, the sponsor was requested to study a minimum of 4 subjects in each of the following 3 age brackets: 6-7 yo, 8-11 yo, and 12 – 17 yo. This second amendment to the written request was dated December 18, 2001.

The sponsor subsequently, submitted a protocol amendment, which had all the required elements, however the sponsor did not want to collect feces for drug analysis. It was decided to not amend the written request a 3rd time, although the sponsor was warned that the lack of feces collection might be problematic and they would be proceeding at their own risk. A summary of the essential features of the pharmacokinetic studies in the 3 written requests and the fulfillment of these features is shown in APPENDIX 1.

3.1 EFFICACY STUDIES

A summary of the pediatric efficacy studies performed is shown in Table 1.

Table 1 Summary of the Pediatric Efficacy Studies

Indication	Protocol #	Study Drug	Study Design
Conduct Disorder with or without MDD or ADD	0600A-126	Venlafaxine IR.	6 week, randomized, double-blind, 2-treatment, dose titration study in 2 patient groups with a placebo lead-in phase and PK substudy. Followed by a 2 year open label safety and preliminary efficacy study.
Major Depressive Disorder	0600B1-382	Venlafaxine ER	8 week, double blind, placebo controlled, efficacy study
	0600B1-394		
	0600B1–395		6 month open label safety study
Generalized Anxiety Disorder	0600B2-396	Venlafaxine ER	8 week, randomized, double-blind, placebo controlled, dose titration study following a 7 ± 3-day single-blind placebo lead-in period. Followed by an optional taper period of up to 2 weeks.
	0600B-397		

3.2 DOSAGES STUDIED

3.2.1 DOSAGES STUDIED IN CONDUCT DISORDER

Initial dosages used in children in the conduct disorder study were weight normalized to the adult dosages.

3.2.1.1 Adult Dosages

A summary of the labeled adult dosages for GAD and MDD are shown in Table 2. Assuming the average adult is 72 kg, the initial starting dose is 75 mg or 1 mg/kg, the average effective dose is 150 mg, or 2 mg/kg, and the maximum-labeled dose for most MDD and GAD is 225 mg, or 3 mg/kg.

Table 2 Summary of Labeled Dosages in Adults for MDD and GAD

Formulation	Indication	Starting Daily Dose	Alternative Starting Dose	Dosage Increment	Maximum Daily Dose	Average Daily Dose
Effexor XR	Depression Moderate Outpatient	75 mg/day	37.5 mg/day for 4 to 7 days	75 mg/day q 4 days – 2 weeks	225 mg/day.	140-180 mg/day
	Generalized Anxiety Disorder	75 mg/day	37.5 mg/day for 4 to 7 days	Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days.	225 mg/day	
Effexor IR	Depression Moderate Outpatient	75 mg/day administered in two or three divided doses, taken with food.		75 mg/day should be made at intervals of no less than 4 days	225 mg/day.	
	Severely Depressed **Inpatients**				Severely depressed patients, may respond to higher doses, up to a maximum of 375 mg/day, generally in three divided doses	350 mg/day (range of 150 to 375 mg/day).

Consequently, the initial dosages studied in pediatric patients in the conduct disorder study were either 1 mg/kg/day or 2 mg/kg/day. These were dosages were administered as immediate release tablets in 2 divided doses 12 hours apart. Each dose was rounded to the nearest 12.5 mg and administered with food according to the Table 3 and Table 4.

Table 3 Venlafaxine (0.5 mg/kg per dose or 1 mg/kg per day)

Weight	Dose per Administration (mg)	Dose per Administration (mg/kg)	Dose per Day (mg/kg)
25.0 – 37.5	12.5	0.33 – 0.50	0.66 - 1.00
37.5 – 62.5	25	0.40 – 0.67	0.80 - 1.34
62.5 – 75.0	37.5	0.50 – 0.60	1.00 - 1.20

Table 4 Venlafaxine (1 mg/kg per dose or 2 mg/kg per day)

Weight	Dose per Administration (mg)	Dose per Administration (mg/kg)	Dose per Day (mg/kg)
25.00 – 31.25	25	0.80 – 1.00	1.60 - 2.00
31.25 – 43.75	37.5	0.86 – 1.20	1.72 - 2.40
43.75 – 56.25	50	0.89 – 1.14	1.78 - 2.28
56.25 – 68.75	62.5	0.91 – 1.11	1.82 - 2.22
68.75 – 75.00	75	1.00 – 1.09	2.00 - 2.18

3.2.2 DOSAGES STUDIED IN MDD AND GAD

As drug exposure as measured by AUC were low compared to historical exposures in adults, the sponsor raised the dose by a factor of 1.5x – 1.67x all subsequent efficacy studies in GAD and MDD using the ER formulation. Consequently, instead of an initial dose of 1 mg/kg, the initial dose was 1.5x higher or 1.5 mg/kg/day. Plus, the typical maintenance dose was expected to be 1.5x 2 mg/kg, or 3 mg/kg/day, and the maximum daily dose was expected to be 1.67x 3 mg/kg or 5 mg/kg/day.

To achieve these weight based dosages in a practical manner, children and adolescents were divided into 3 weight categories and the ER formulation was dosed once daily in the morning with food. Dosages by pediatric patient weight group for the efficacy studies are shown in Table 5.

Table 5 Doses by Pediatric Patient Weight Group for MDD, GAD, and PK Studies with Effexor ER

Body Weight Range	Dose (mg)		Average Dose (mg/kg)	Dose Range (mg/kg)
	Minimum[a]	Maximum		
25-39 kg	37.5	112.5	2.7	1.0 – 4.5
40-49 kg	75	150	2.6	1.5 – 3.75
≥50 kg	75	225	3.0	1.5 – 4.5

a All patients received 37.5 mg/day during the first week; doses were in the indicated range after week 1.

4 PEDIATRIC PHARMACOKINETICS

Two pediatric pharmacokinetic studies were conducted with venlafaxine.

Table 6 Summary of the Pediatric Pharmacokinetic Studies

Indication	Protocol #	Study Drug	Age Groups	Study design	Dose	Analytes	Matrices
Conduct Disorder with or without MDD or ADD	0600A-126-US	Venlafaxine IR	Children & Adolescents 6 – 15 yo	MD to SS BID	1 or 2 mg/kg/day	V ODV	Plasma
ADD or ADHD	0600B1-169-US	Venlafaxine ER	6 - 7 yo 8 - 11 yo 12 - 17 yo	SD	Ave 1.5 range 0.96 – 2.17 mg/kg	V ODV NDV NODV & glucuronides	Plasma Urine

Complete results are shown in APPENDIX 2.

In the study with IR tablets mean Clearance/F is approximately 2 – 3 L/hr/kg. For the ER capsules mean clearance even though adjusted for urinary recovery (~50%) is still about 2 L/hr/kg. In some individuals clearance is much lower, e.g. 0.96 L/hr/kg and likely reflects CYPIID6 poor metabolizers.

Mean volume of distribution and half-lives are approximately 10 L/kg and 2.5 – 5 hours in the steady-state study with the IR tablets. The longer half-lives reflecting the poor metabolizers, and as the volume of distribution is erroneously calculated as V = Cl/F / kel, it also reflects metabolism.

For the ER capsules the longer half-lives reflect the absorption kinetics of 'flip-flop' kinetics and are not reflective of elimination. In addition, the reported volumes of distribution are much higher, and although the method of calculation was not mentioned, if either the same method was used or if statistical moments were used without correction for absorption we would expect that the volume estimates would be erroneously high.

Because of the above factors, the variability in the data, and the small number of subjects no clear pattern emerges from simply examining the raw data. However, when AUCs are normalized by dose and plotted by age a clear pattern emerges, (see Figure 1 and Figure 2).[1],[2],[3]

In Figure 1 and Figure 2 we see that dose normalized AUCs are lower in adolescents than in adults and even lower in preadolescents and younger children.

Based upon the smoothing curves we might expect that children depending on age may need a 2-4 fold higher dose on a mg/kg/basis as compared to adults, and adolescents needing only a higher slightly higher mg/kg/dose as compared to adults. With the caveat that the exposures to the active metabolites, NDV and NODV, were not considered.

Approximate dose normalized AUC ratios for the ER formulation in children (Tanner Stage $\leq$ 3) and adolescents (Tanner Stage > 3) are shown in Table 7.

[1] AUC data from adults represent mean AUCs from studies reported in NDA 20-699 vs. and estimated mean age of 30 years old.
[2] For the ER capsules data from an outlier with a venlafaxine AUC of > 7000 and no detectable ODV is not shown.
[3] Smoothing functions are cubic splines for the IR tablets and LOESS curves for the ER capsules

Table 7 Approximate Dose Normalized AUC ratios for the Effexor

	Approximate Mean AUCs		AUC Ratios	
	Children	**Adults**	**Children to Adults**	**Adults to Children**
Venlafaxine	250	1000	0.25	4.00
ODV	1250	2500	0.50	2.00
V + ODV'	1250	3400	0.37	2.72
	Adolescents	**Adults**	**Adolescents to Adults**	**Adults to Adolescents**
Venlafaxine	250	1000	0.25	4.00
ODV	1750	2500	0.70	1.43
V + ODV'	2000	3500	0.57	1.75

Based on Table 7 preadolescent children should probably receive an 3 fold higher dose on average (range 2 – 4 fold) as compared to adults on a mg/kg basis. In addition, adolescents should probably receive approximate a 1.75 fold higher dose on a mg/kg basis as compared to adults.

Since the average dose in adults is 2 mg/kg, this translates into a dose of 4 – 8 mg/kg (average 6 mg/kg) in preadolescent children of various ages, and a dose of about 3.5 mg/kg in adolescents. In addition, a check of the analytical quality control samples indicates that the measured AUCs are slightly greater than the true values, thus these dose adjustments might even need to be 5-10% higher. From Table 5 we see that although the dosing adolescents may have been adequate in the efficacy studies, the dosing in preadolescent children and especially younger children was likely subtherapeutic.

Unfortunately, the reason for the difference in exposures with age is not clear, even though there is a trend for lower recovery with lower age possibly indicating some truncation in absorption. Unfortunately, the sponsor did not follow OCPB's recommendation to determine fecal recovery.

In the adult mass balance study, approximately 87% of the dose were recovered in the urine over 48 hours and a similar degree of recovery would be expected in children. Although the fraction of the dose recovered as venlafaxine and ODV in the urine from children dosed with the ER formulation was similar to the fractions recovered in adults, (see Table 13), very little was recovered as the glucuronide conjugates in children as compared to in adults. Consequently, the mean total 48 hour recovery ranged from 41% to 57% in children and adolescents with the percent recovery increasing with age. Urinary recoveries were also supposed to be determined in the study with the IR tablets, however, the samples were stored too long and analysis could not be performed for stability reasons.[4]

In the present submission glucuronide conjugates were determined by recoveries both pre and post incubation with β-glucuronidase. Unfortunately, a positive control for β-glucuronidase activity was not included. In addition, the original mass balance study used a 9:1 mixture of β-glucuronidase:sulfatase in the presence and absence of a proposed β-glucuronidase inhibitor. Thus without additional information the basis of this discrepancy can't be determined.

[4] Personal communications with sponsor.

Figure 1

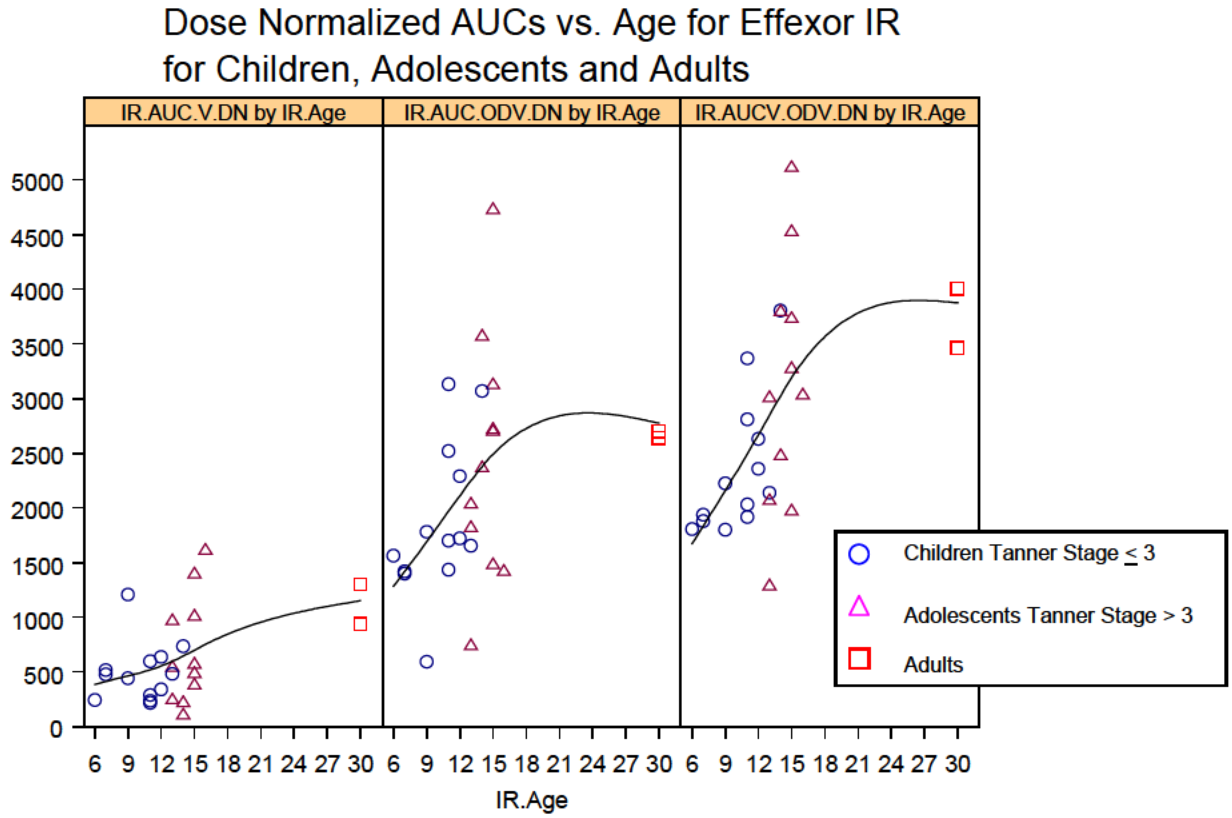
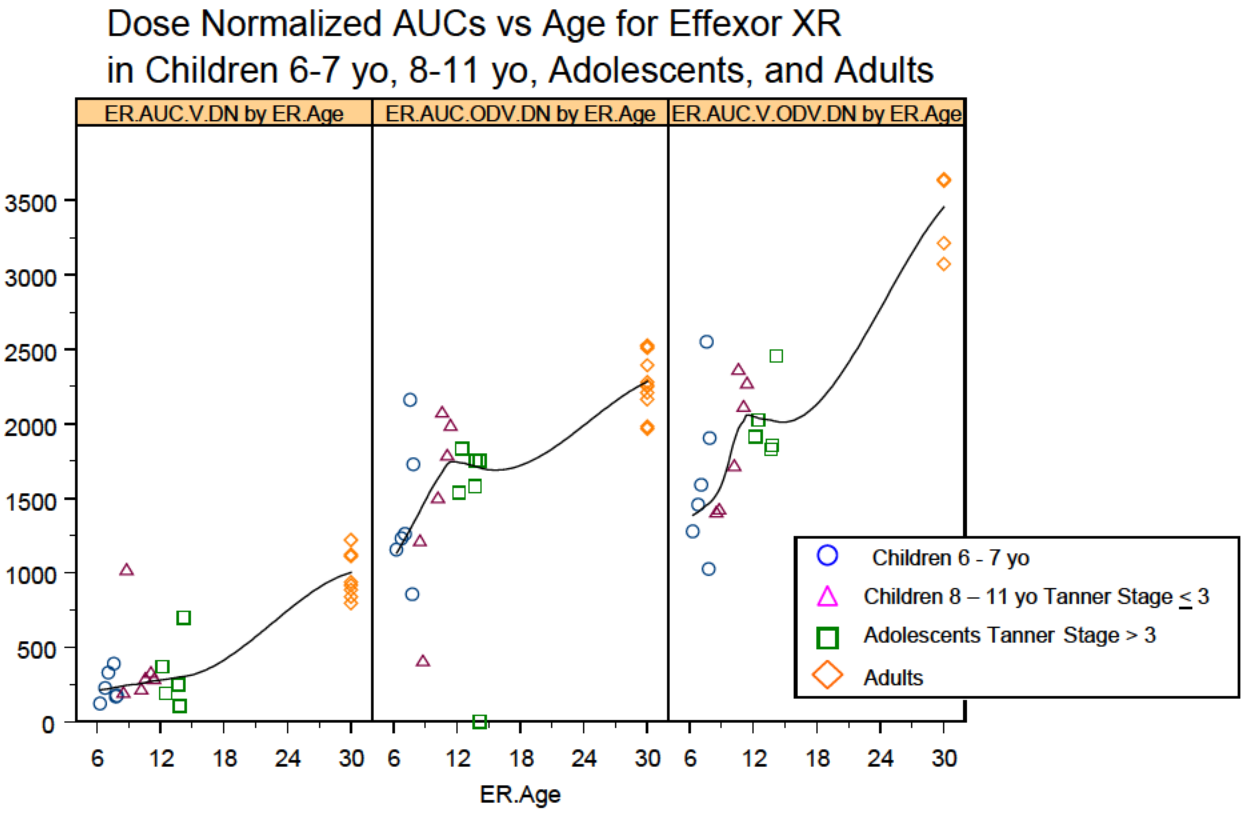


Figure 2



APPENDIX 1 Summary of Pediatric Written Requests and Fulfillment of Features

Pediatric PK Study - Original Written Request & Revisions				PK Studies - Fulfillment of WR		
April 28, 1999		July 7, 2000	December 18, 2001	Study 600A	Study 600B	Reviewer assessment regarding sufficient achievement of WR requirements
Subject Population						**Yes**
MDD	GAD - Only differences Listed	MDD	Any Pediatric Population	Conduct Disorder	Y	
Provide information pertinent to dosing of the study drug in he relevant pediatric population				Y 0.66-2.4 mg/kg/day n 2 divided doses	Y	
			Effexor XR 1 SD PK study using the full range of pediatric dosing in any pediatric popula ion		Y- 37.5 & 75 mg potentially low exposure in younger patients	
Study Design						**Yes**
Traditional PK or Pop PK			Tradi ional	Traditional	Traditional	Pop PK would not be useful for XR
Demographics						**Yes - When data combined across studies**
Children 7 - 11	6-17 yo give or take a year. Should include subjects from the entire age range	Children 7 - 12		Y?		
Adolescents 12 -17		Adolescents 13 - 17				
equally represented				Y	Y	
Reasonable distribution of both sexes				?Y	?Y	
			Children 6 - 11		Y	
			Adolescents 12 - 17		Y	
			4 completers in 6 - 7 yo		Y	
			4 completers in 8 - 11 yo		Y	
Sample Size						**Yes**
Sufficient number of subjects to adequately characterize the PK in the above age groups				Y?	Y	
Sampling of Biological Matrixes						**Yes - see below under Analytes & PK Metrics**
PK measurements as appropriate				0, 0.5, 1, 1.5, 2, 3, 4,6, 8, 12, 28, 42, 56 hours	-0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48 hours	
Statistical Analysis						**Yes**
Descriptive Analysis of the Pharmacokinetic Parameters				Mean, SD, CV, GM, Min, Max	Mean, SD, CV, GM, Min, Max	
			Estimate Clcr normalized to weight & BSA and evaluate relationship to venlafaxine and metabolite elimination		Y	
Analytes & Pharmacokinetic Metrics						**Yes**
Study Drug				Venlafaxine	Venlafaxine	
Any metabolites that makes substantial contributions to safety or efficacy				ODV	ODV	
AUC				Y	Y	
half-life				Y	Y	
Cmax				Y	Y	
Tmax				Y	Y	
Clpo in peds in the relevant age range				Y	Y	
			Urine (see below)			
			Venlafaxine		Y	
			ODV		Y	
			Conjugated ODV		Y	
			Other Metabolites		Y	
			≥90% recovery		N - However, historical data from adults suggests that > 85% urinary recovery is possible within 48 hours.	
			Intervals sufficiently shot to estimate if absorption is truncated before 24 hours		N	
			Feces Collection suggested		N	
			Feces analysis if o her data suggests truncation of absorption		N	
Formulations Studied						**Yes**
Age appropriate formulations - "your marketed solid dosage formulation should be adequate for hese studies"				12.5 mg, 25 mg, 50 mg caps	37.5 mg & 75 mg XR Caps	
Report						**Yes - Very Nice**
Format - full report or analyses not previously submitted to the agency				Y	Y	

APPENDIX 2 Venlafaxine Pharmacokinetic Metrics in Children and Adolescents

Table 8 Effexor (IR Tablets) Venlafaxine Pediatric Steady State Pharmacokinetics (Study 0600A-126-US) [a]

Dose Group	Age Group (n)	CMAX (NG/ML)	TMAX (H)	T1/2 (H)	AUC12 (ng/ml x Hr^{-1})	CL/F (L/H/KG)	CL/F (L/H)	VZ/F (L/KG)	VZ/F (L)
1 mg/kg/day	Child (n = 6)	38.1 ± 10.9 (28.5) 20.5 - 49.5 [38.65]	2.5 ± 0.8 (33.5) 1 - 3 [3]	2.4 ± 0.5 (19.7) 1.84 - 3 [2.62]	183.8 ± 67.6 (36.8) 85 - 260 [177]	3.1 ± 1.5 (46.4) 1.92 - 5.85 [2.83]	92.6 ± 52.4 (56.6) 44.6 - 186.1 [82.35]	10.3 ± 2.9 (28.1) 7.48 - 15.64 [9.755]	306.7 ± 134.5 (43.9) 174 - 497 [279.5]
	Adolescents (n = 6)	59.5 ± 35.3 (59.4) 17.4 - 124 [53.1]	1.7 ± 0.4 (24.5) 1 - 2 [1.75]	3.5 ± 1.2 (33.8) 1.58 - 5.02 [3.73]	297.5 ± 207.5 (69.7) 45 - 673 [261.5]	3.3 ± 3.9 (119.5) 0.74 - 11.13 [1.93]	204.6 ± 236.9 (115.8) 57.9 - 683.7 [119.9]	11.7 ± 7.1 (60.5) 5.38 - 25.44 [9.665]	746.0 ± 416.4 (55.8) 420 - 1562 [620.5]
2 mg/kg/day	Child (n = 7)	109.0 ± 47.0 (43.1) 44.8 - 183 [101]	2.5 ± 1.0 (41.6) 1 - 4 [3]	3.3 ± 0.6 (19.7) 2.26 - 4.27 [3.23]	597.1 ± 278.3 (46.6) 203 - 1041 [700]	2.2 ± 1.4 (62.8) 0.96 - 4.92 [1.43]	76.4 ± 37.5 (49.1) 27.7 - 140.7 [70.9]	9.4 ± 4.1 (43.7) 5.92 - 16.05 [6.58]	342.4 ± 142.2 (41.5) 171 - 576 [330]
	Adolescents (n = 5)	124.9 ± 83.8 (67.1) 45.5 - 246 [122]	2.4 ± 0.5 (22.8) 2 - 3 [2]	5.2 ± 2.0 (39.0) 2.24 - 7.4 [5.08]	806.6 ± 614.9 (76.2) 206 - 1711 [901]	2.3 ± 1.9 (84.5) 0.58 - 4.86 [1.11]	128.8 ± 94.1 (73.1) 34.2 - 262.9 [90]	13.1 ± 7.6 (58.2) 5.57 - 24.89 [11.85]	768.8 ± 351.2 (45.7) 326 - 1200 [849]

a Values are Mean ± SD (CV) Range and [Median]

Table 9 Effexor (IR Tablets) O-Desmethyl-Venlafaxine Pediatric Steady State Pharmacokinetics (Study 0600A-126-US) [a]

Dose Group	Age Group (n)	CMAX (NG/ML)	TMAX (H)	T1/2 (H)	AUC12 (ng/ml x Hr^{-1})	CL/F (L/H/KG)	CL/F (L/H)	VZ/F (L/KG)	VZ/F (L)
1 mg/kg/day	Child (n = 6)	106.1 ± 38.7 (36.5) 79.9 - 179 [86.35]	3.0 ± 1.1 (36.5) 1 - 4 [3]	7.7 ± 2.5 (31.9) 5.16 - 12.33 [7.29]	889.5 ± 348.9 (39.2) 664 - 1575 [735.5]	0.6 ± 0.2 (26.3) 0.32 - 0.75 [0.68]	17.3 ± 5.2 (30.0) 11.3 - 23.9 [16.5]	7.0 ± 3.5 (50.5) 3.57 - 13.4 [6.83]	201.5 ± 117.7 (58.4) 84 - 426 [173]
	Adolescents (n = 6)	155.0 ± 90.4 (58.3) 47.1 - 311 [160.5]	1.9 ± 0.2 (10.6) 1.5 - 2 [2]	8.2 ± 1.8 (22.5) 4.96 - 10.34 [8.625]	1278.3 ± 792.0 (62.0) 443 - 2688 [1153]	0.5 ± 0.3 (62.7) 0.19 - 1.13 [0.44]	33.9 ± 19.6 (57.8) 12.2 - 70.7 [30.05]	6.4 ± 4.6 (71.2) 1.98 - 14.67 [4.875]	408.0 ± 273.9 (67.1) 130 - 920 [376]
2 mg/kg/day	Child (n = 7)	221.5 ± 100.6 (45.4) 53.3 - 326 [207]	3.1 ± 1.4 (46.5) 1.5 - 6 [3]	8.5 ± 1.2 (14.0) 6.73 - 10.06 [8.2]	1979.9 ± 866.4 (43.8) 511 - 3009 [1913]	0.69 ± 0.6 (83.1) 0.33 - 1.96 [0.52]	24.1 ± 15.7 (65.0) 10.6 - 56.4 [18.9]	8.22 ± 6.4 (77.4) 4.55 - 22.27 [5.78]	290.4 ± 176.8 (60.9) 130 - 641 [244]
	Adolescents (n = 5)	235 ± 90.2 (38.4) 153 - 382 [197]	3.2 ± 0.8 (26.1) 2 - 4 [3]	13.0 ± 4.1 (31.8) 7.36 - 18.97 [13.2]	2236 ± 714.1 (31.9) 1505 - 3310 [1899]	0.48 ± 0.1 (28.9) 0.3 - 0.66 [0.53]	29.9 ± 10.9 (36.5) 16.3 - 43 [25.8]	9.4 ± 4.4 (47.0) 3.21 - 14.5 [9.2]	606.8 ± 376.8 (62.1) 174 - 1176 [499]

a Values are Mean ± SD (CV) Range and [Median]

Table 10 Effexor (IR Tablets) Pediatric Steady State Pharmacokinetics Combined Venlafaxine and O-Desmethyl-Venlafaxine Exposures (Study 0600A-126-US)[a]

Dose	Age Group	AUC_{0-12} (ng/ml x hr^{-1})			Ratio ODV:V
		Venlafaxine	O-Desmethyl-venlafaxine	ODV + V	
1 mg/kg/day	Children (n = 6)	183.8 ± 67.6 (36.8) 85 - 260 [177]	889.5 ± 348.9 (39.2) 664 - 1575 [735.5]	1073.3 ± 354.0 (33.0) 749 - 1756 [995]	5.4 ± 2.6 (47.1) 2.7 - 8.7 [5.2]
	Adolescents (n = 6)	297.5 ± 207.5 (69.7) 45 - 673 [261.5]	1278.3 ± 792.0 (62.0) 443 - 2688 [1153]	1575.8 ± 833.1 (52.9) 768 - 2907 [1317]	7.5 ± 7.9 (105.3) 1.4 - 21.6 [3.9]
2 mg/kg/day	Children (n = 7)	597.1 ± 278.3 (46.6) 203 - 1041 [700]	1979.9 ± 866.4 (43.8) 511 - 3009 [1913]	2577 ± 730.7 (28.4) 1552 - 3729 [2620]	4.7 ± 4.2 (88.9) 0.5 - 13.3 [3.4]
	Adolescents (n = 5)	806.6 ± 614.9 (76.2) 206 - 1711 [901]	2236 ± 714.1 (31.9) 1505 - 3310 [1899]	3042.6 ± 580.5 (19.1) 2156 - 3536 [3216]	5.8 ± 6.2 (107.1) 0.9 - 16.1 [2.7]

a Values are Mean ± SD (CV) Range and [Median]

Table 11 Effexor ER Venlafaxine Pediatric Single Dose Pharmacokinetics (Study 0600B1-129-US) [a,b]

Age Group	CMAX (NG/ML)	TMAX (H)	T1/2 (H)	AUC∞ (ng/ml x Hr^{-1})	CL/F (L/H/KG)	Vz/F (L/KG)	CL[b] (L/H/KG)	CL[b] (L/H)	Vz[b] (L/KG)	Vz[b] (L)
6- 7 YEAR OLD	6	6	6	6	6	6	6	6	6	6
	29.3 ± 13.5 (45.9) 11 - 49.1 [28.55]	4.3 ± 0.8 (18.8) 4 - 6 [4]	9.9 ± 3.6 (35.9) 5.8 - 14.35 [9.8]	381.2 ± 182.0 (47.8) 202 - 604 [361.5]	5.0 ± 2.1 (41.9) 2.57 - 8.19 [5.0]	72.2 ± 49.6 (68.8) 33.65 - 169.64 [53.2]	2.09 ± 1.14 (54.74) 0.90 - 3.75 [1.97]	52.40 ± 21.62 (41.27) 24.64 - 85.19 [46.46]	31.87 ± 26.36 (82.71) 11.54 - 77.70 [18.97]	760.8 ± 516.0 (67.8) 424.5 – 1763.7 [526.2]
8 – 11 YEAR OLD	6	6	6	6	6	6	6	6	6	6
	37.2 ± 19.7 (52.8) 19.8 - 75.9 [32]	4.7 ± 1.0 (22.1) 4 - 6 [4]	8.1 ± 2.3 (28.6) 5.34 - 10.93 [8.47]	520.5 ± 385.8 (74.1) 216 - 1292 [405.5]	3.5 ± 1.5 (41.9) 0.98 - 5.16 [3.5]	38.5 ± 15.1 (39.1) 12.09 - 55.37 [38.5]	1.79 ± 1.00 (55.69) 0.37 - 2.79 [2.11]	70.74 ± 38.80 (54.85) 10.99 - 113.62 [81.16]	20.0 ± 12.7 (63.34) 4.58 - 41.47 [19.42]	778.8 ± 426.9 (54.8) 135.3 – 1379.1 [739.2]
12- 17 YEAR OLD	6	6	6	6	6	6	6	6	6	6
	48.3 ± 38.5 (79.7) 16.6 - 120.7 [35.4]	6.3 ± 2.9 (46.5) 4 - 12 [6]	13.7 ± 14.6 (107.2) 3.95 - 41.99 [7.7]	1929.7 ± 3615.2 (187.3) 137 - 9282 [385]	3.8 ± 3.3 (86.7) 0.13 - 9.53 [3.35]	34.2 ± 18.9 (55.2) 8.16 - 64.6 [34.4]	2.33 ± 1.87 (80.17) 0.03 - 5.19 [2.17]	114.07 ± 105.28 (92.30) 1.63 - 297.57 [89.62]	20.3 ± 10.8 (53.18) 1.66 - 35.2 [21.02]	981.3 ± 620.9 (63.3) 100.0 - 2017.6 [871.9]

a Values are Mean ± SD (CV) Range and [Median]
b Adjusted for Drug Recovery in the Urine

Table 12 Effexor ER O-Desmethyl-venlafaxine Pediatric Single Dose Pharmacokinetics (Study 0600B1-129-US) [a]

Age Group	CMAX (NG/ML)	TMAX (H)	T1/2 (H)	AUC∞ (ng/ml x Hr^{-1})	CL/F (L/H/KG)	Vz/F (L/KG)	ADV + V AUC∞	Ratio AUC_{∞}^{ODV} / AUC_{∞}^{V}
6- 7 YEAR OLD	6	6	6	6	6	6	6	6
	93.2 ± 24.3 (26.1) 62.3 - 122.8 [94.7]	7.3 ± 1.0 (14.1) 6 - 8 [8]	10.7 ± 2.2 (20.6) 8.22 - 13.69 [10.6]	2198.3 ± 629.8 (28.7) 1156 - 2960 [2249.5]	0.8 ± 0.2 (31.6) 0.46 - 1.17 [0.8]	11.5 ± 2.0 (17.1) 8.6 - 14.41 [11.8]	2579.5 ± 769.2 (29.8) 1385.0 - 3494.0 [2663.5]	6.5 ± 2.5 (38.2) 3.8 - 9.8 [5.5]
8 – 11 YEAR OLD	6	6	6	6	6	6	6	6
	92.2 ± 50.0 (54.3) 20.7 - 164.7 [104.3]	7.0 ± 1.1 (15.6) 6 - 8 [7]	11.8 ± 2.4 (20.7) 7.96 - 15.37 [11.6]	2094.5 ± 957.8 (45.7) 514 - 2923 [2467.5]	0.9 ± 0.8 (84.1) 0.48 - 2.47 [0.62]	15.6 ± 12.9 (82.6) 5.54 - 41.1 [11.2]	2615.0 ± 747.1 (28.6) 1572.0 - 3328.0 [2869.5]	5.5 ± 2.6 (46.9) 0.4 - 7.2 [6.6]
12- 17 YEAR OLD	5	5	5	5	5	5	6	6
	94.1 ± 32.9 (35.0) 51.3 - 137.3 [86.9]	8.4 ± 3.3 (39.1) 6 - 12 [6]	13.1 ± 3.6 (27.4) 8.02 - 16.84 [14.36]	2446.8 ± 638.0 (26.1) 1478 - 3226 [2606]	0.6 ± 0.0 (7.8) 0.54 - 0.65 [0.57]	11.1 ± 3.0 (27.1) 7.34 - 13.87 [12.55]	3968.7 ± 2694.3 (67.9) 1835.0 - 9282.0 [3292.5]	6.5 ± 6.0 (91.3) 0.0 - 16.7 [5.2]

a Values are Mean ± SD (CV) Range and [Median]

Table 13 Urinary Recovery (% of Dose) and Percent Recovered as 'Conjugate' (%C) (Study 0600B1-129-US and Adult Mass Balance Study) [a]

Age Group	Venlafaxine			O-Desmethyl-Venlafaxine			N-Desmethyl-Venlafaxine			N,O-Didesmethyl-Venlafaxine			All 4 Analytes			Metabolites other than V& ODV
	Unconjugated 0 - 48h	Total 0 - 48 h	%C	Unconjugated 0 - 48h	Total 0 - 48 h	%C	Unconjugated 0 - 48h	Total 0 - 48 h	%C	Unconjugated 0 - 48h	Total 0 - 48 h	%C	Unconjugated 0 - 48h	Total 0 - 48 h	%C	
	6	6	6	6	6	6	6	6	4	6	6	6	6	6	6	6
6- 7 YEAR OLD	2.8 ± 1.3 (46.9) 1.3 - 4.3 [2.9]	2.5 ± 1.2 (49.6) 1.2 - 4 [2.3]	-12.2 ± 22.4 (-184.0) -57.1 - 0.0 [-3.8]	28.5 ± 6.7 (23.30) 20.3 - 36.6 [28.65]	31.1 ± 9.5 (30.7) 20.1 - 47 [29.35]	5.4 ± 19.2 (357.8) -26.2 - 22.1 [14.8]	0.2 ± 0.2 (121.6) 0 - 0.5 [0.1]	0.3 ± 0.3 (103.3) 0 - 0.9 [0.3]	25.0 ± 50.0 (200.0) 0 - 100 [0]	7.3 ± 2.5 (34.9) 4.6 - 11.6 [7.45]	7.6 ± 3.8 (49.2) 4 - 14.4 [6.8]	-1.5 ± 24.1 (-1588.3) -44.4 - 19.4 [9.0]	38.8 ± 9.3 (23.9) 28.1 - 52.2 [38.2]	41.5 ± 14.1 (33.8) 25.3 - 66.3 [38.75]	3.1 ± 19.9 (631.2) -30.7 - 21.3 [12.9]	8.0 ± 4.0 (50.4) 4.0 – 15.3 [7.2]
	6	6	6.0	6	6	6	6	6	5	6	6	6	6	6	6	6
8- 11 YEAR OLD	5.1 ± 3.7 (72.1) 1.3 - 12.1 [4.1]	4.7 ± 3.6 (76.6) 1.2 - 11.7 [3.75]	-9.6 ± 6.6 (-68.3) -18.8 - -2.6 [-8.4]	26.7 ± 15.8 (59.0) 6.9 - 51.6 [27.4]	33.0 ± 17.9 (54.2) 9.7 - 57.1 [31.6]	20.8 ± 10.5 (50.6) 7.0 - 31.8 [23.7]	2.2 ± 3.6 (167.5) 0 - 9.5 [0.7]	2.1 ± 3.6 (166.5) 0 - 9.3 [0.75]	-3.2 ± 13.2 (-412.9) -25.0 - 11.1 [0.0]	8.7 ± 4.7 (53.4) 1.2 - 14.2 [9.55]	10.5 ± 5.2 (49.3) 2 - 16.9 [12.15]	20.2 ± 12.6 (62.6) 3.2 - 40.0 [17.0]	42.7 ± 17.0 (39.9) 16 - 67.9 [45.55]	50.3 ± 19.0 (37.8) 21.9 - 74.9 [51]	15.7 ± 9.9 (63.1) 4.4 - 28.2 [12.8]	12.6 ± 5.7 (45.3) 2.0 – 18.5 [13.2]
	6	6	6.0	6	6	6	6	6	5	6	6	5	6	6	6	6
12- 17 YEAR OLD	6.5 ± 6.1 (94.3) 1.1 - 18 [4.1]	6.5 ± 6.3 (95.9) 1 - 18.2 [3.95]	-2.1 ± 6.6 (-321.4) -11.1 - 3.0 [1.7]	29.9 ± 16.4 (55.0) 0.1 - 48.9 [33.2]	37.7 ± 21.2 (56.1) 0.2 - 64.2 [42.85]	25.2 ± 13.2 (52.3) 11.7 - 50.0 [22.8]	1.2 ± 1.0 (81.1) 0 - 2.5 [1.25]	1.2 ± 1.0 (82.4) 0 - 2.5 [1.1]	-3.0 ± 9.7 (-324.9) -20.0 - 5.0 [0.0]	9.2 ± 5.5 (59.3) 0 - 14.9 [9.65]	11.5 ± 6.7 (58.6) 0 - 17.1 [12.75]	19.6 ± 5.6 (28.6) 12.4 - 27.8 [19.9]	46.8 ± 15.4 (32.8) 20 - 65.5 [47.95]	56.9 ± 21.7 (38.2) 20.4 - 85.4 [55.1]	15.3 ± 8.0 (52.0) 2.0 - 23.3 [16.9]	12.7 ± 6.8 (54.1) 2.0 – 19.6 [13.3]
				5	5	5										
				35.9 ± 8.4 (23.5) 26.2 - 48.9 [34.6]	45.2 ± 11.7 (25.9) 31.9 - 64.2 [42.9]	20.2 ± 5.6 (27.8) 11.7 - 25.9 [21.7]										
Adult Mass Balance Study		5%		29%	55%									87%		

a Values are Mean ± SD (CV) Range and [Median]

APPENDIX 3 Mean Venlafaxine AUCs in Adults

Table 14 Venlafaxine AUCs in Adults from NDA 20-699 March 3, 1977

Study	Dosage Form	Dose	Mean Values					Mean Values Normalized to a 1 mg/kg dose			
			AUCv	AUCodv	AUCcomb	NDV	Ratio	AUCv	AUCodv	AUCcomb	Ratio
600-B-143-UK	ER	2 x 75 mg	1775	4516	6147		2.54	887.5	2258	3073.5	2.54
	ER	150 mg	1777	4787	6425		2.69	888.5	2393.5	3212.5	2.69
	IR Tab	50 mg	625	1758	2308		2.81	937.5	2637	3462	2.81
600-B-136-US	IR Tab	150 mg	2604	5402	8014		2.07	1302	2701	4007	2.07
	ER	2 x 75 mg	2246	5036	7284		2.24	1123	2518	3642	2.24
	ER	2 x 75 mg	2240	5019	7260		2.24	1120	2509.5	3630	2.24
	ER	150 mg	2222	5052	7275		2.27	1111	2526	3637.5	2.27
600-B-145-US	ER	150 mg fasted	1834	4418			2.41	917	2209		2.41
	ER	150 mg fed	1877	4331			2.31	938.5	2165.5		2.31
600-B-138-US	ER	75 mg fasted	841	1967			2.34	841	1967		2.34
	ER	75 mg fed	797	1982			2.49	797	1982		2.49
600-B-139-US	ER	75 mg AM	1220	2251			1.85	1220	2251		1.85
	ER	75 mg PM	1222	2281			1.87	1222	2281		1.87
600-A-131-US	IR Tab	75 mg q 12h EM	1082	2876	3963	190	2.66				
	IR Tab	75 mg q 12h PM	3487	915	4405	1319	0.26				
n								13	13	7	13
Mean ± SD (CV) range [median]								1023.5 ± 165.8 (16.2) 797.0 - 1302.0 [938.5]	2338.3 ± 232.6 (9.9) 1967.0 - 2701.0 [2281.0]	3523.5 ± 309.6 (8.8) 3073.5 - 4007.0 [3630.0]	2.3 ± 0.3 (12.3) 1.8 - 2.8 [2.3]

APPENDIX 4 Subject Demographics in Pediatric Pharmacokinetic Studies

Table 15 Subject Demographics – Study 600A – Effexor IR

Protocol 600A IR Capsules																	
Subject #	Child or Adolescent	Age (yrs)	Gender	Weight (kg)	Dose			Subject #	Child or Adolescent	Age (yrs)	Gender	Weight (kg)	Dose		
					mg	Nominal (mg/kg)	mg/kg						mg	Nominal (mg/kg)	mg/kg
2	C	**7**	M	23.2	12.5	0.5	0.54	1	C	13	M	51	50	1	1.02
26	C	**6**	M	21	12.5	0.5	0.60	3	C	11	M	31.8	37.5	1	0.85
28	C	**7**	F	25.2	12.5	0.5	0.50	25	C	10	M	28.6	25	1	1.14
32	C	11	F	31.8	12.5	0.5	0.39	27	C	12	M	32.7	37.5	1	0.87
33	C	11	M	40.4	25.0	0.5	0.62	29	C	9	M	28.8	25	1	1.15
34	C	9	M	31.8	12.5	0.5	0.39	30	C	12	M	44.5	50	1	0.89
								43	C	13	M	43.4	37.5	1	1.16
13	A	13	M	61.4	25.0	0.5	0.41	14	A	16	F	58.6	62.5	1	0.94
37	A	15	M	78	37.5	0.5	0.48	38	A	14	M	66.4	62.5	1	1.06
39	A	15	M	65.5	37.5	0.5	0.57	40	A	13	F	48.2	50	1	0.96
41	A	14	M	76.1	37.5	0.5	0.49	44	A	12	F	54.1	50	1	1.08
42	A	14	M	50.5	25.0	0.5	0.50	45	A	13	M	81.1	75	1	1.08
46	A	13	M	62.7	37.5	0.5	0.60								

Table 16 Subject Demographics – Study 600B – Effexor ER Capsules

PROTOCOL 0600B1-169-US														
SUBJECT	Age (yrs)	Ht (cm)	Wt (kg)	BSA (m2)	BMI (kg/m2)	Gender	Race	Dose		CYP2D6		ClCr		
								(mg)	(mg/kg)	Genotype	Predicted Phenotype*	(L/hr)	(L/hr/kg)	(L/hr/m2)
6-7 year old														
9	7.8	(b) (4)				Male	Black	37.5	1.35	wt/wt	EM	13.2	0.476	13.0
14	7.9					Male	Black	37.5	1.27	wt/wt	EM	2.1	0.071	2.0
15	6.3					Male	Black	37.5	1.65	wt/wt	EM	5.8	0.257	6.7
16	7.6					Male	Black	75	1.83	wt/wt	EM	4.2	0.102	3.4
17	6.8					Female	White	37.5	1.37	wt/wt	EM	10.8	0.397	11.1
18	7.1					Male	White	37.5	2.17	wt/wt	EM	5.0	0.289	6.8
MEAN	7.3	124.6	27.6	0.97	17.5									
SD	0.6	7.6	7.9	0.16	3.7									
%CV	8.7	6.1	28.7	16.7	21.1									
8-11 year old														
2	8.8	(b) (4)				Male	White	37.5	1.27	*4/*4	PM	3.3	0.113	3.3
3	11.4					Male	White	75	1.32	wt/wt	EM	7.6	0.134	4.8
4	8.5					Male	White	37.5	1.43	wt/wt	EM	6.3	0.238	6.5
5	11.1					Male	White	37.5	1.12	*4/wt	EM	5.6	0.165	4.9
12	10.6					Male	White	75	1.41	wt/wt	EM	2.4	0.045	1.6
19	10.2					Male	White	75	1.72	wt/wt	EM	4.8	0.109	3.6
MEAN	10.1	141.0	40.5	1.25	19.9									
SD	1.2	12.8	12.7	0.25	3.1									
%CV	11.9	9.1	31.4	20.2	15.5									
12-17 year old														
6	13.7	(b) (4)				Male	White	75	1.65	wt/wt	EM	8.9	0.197	6.3
7	14.2					Male	White	75	1.25	*4/*4	PM	4.2	0.069	2.5
8	14.2					Male	White	75	1.5	*4/wt	EM	6.3	0.125	4.2
10	13.8					Female	White	75	1.31	wt/wt	EM	4.9	0.085	3.0
11	12.2					Female	White	37.5	0.96	wt/wt	EM	4.2	0.107	3.2
13	12.5					Male	White	75	1.76	wt/wt	EM	4.2	0.098	3.1
MEAN	13.4	161.0	49.1	1.48	18.8									
SD	0.9	6.9	8.3	0.16	1.8									
%CV	6.5	4.3	16.9	10.5	9.6									

* A Predicted Phenotype of EM= Extensive Metabolizer and PM= Poor Metabolizer.

Table 17 Demographics – Effexor (IR Tablets) Pediatric Steady State Pharmacokinetics (Study 0600A-126-US) [a]

Dose Group	Age Group (n)	Age	Weight (kg)	Height (cm)	BSA (m^2)	Sex (M/F)	Race (W/B/A/O)
1 mg/kg/day	Child (n = 6)	8.5 ± 2.2 (25.5) 6 - 11 [8]	28.8 ± 7.1 (24.8) 21 - 40 [28.5]	132.5 ± 10.7 (8.1) 116 - 144 [133]	1.03 ± 0.16 (16.0) 0.82 - 1.26 [1.02]	5/1	5/1/0/0
	Adolescents (n = 6)	14.5 ± 0.8 (5.8) 13 - 15 [15]	65.8 ± 10.0 (15.2) 51 - 78 [64.5]	159.5 ± 24.0 (15.1) 112 - 180 [165]	1.70 ± 0.20 (11.66) 1.43 - 1.97 [1.68]	6/0	6/0/0/0
2 mg/kg/day	Child (n = 7)	11.71 ± 1.6 (13.7) 9 - 14 [12]	37.43 ± 8.8 (23.5) 29 - 51 [33]	148.86 ± 14.7 (9.8) 130 - 168 [149]	1.24 ± 0.2 (14.5) 1.02 - 1.45 [1.22]	7/0	7/0/0/0
	Adolescents (n = 5)	14.2 ± 1.3 (9.2) 13 - 16 [14]	61.6 ± 12.7 (20.6) 48 - 81 [59]	164.6 ± 7.8 (4.7) 155 - 173 [163]	1.67 ± 0.2 (12.3) 1.44 - 1.97 [1.62]	2/3	5/0/0/0

a Values are Mean ± SD (CV) Range and [Median]

Table 18 Demographics – Effexor ER Pediatric Single Dose Pharmacokinetics (Study 0600B1-129-US) [a]

Age Group	AGE (yrs)	HEIGHT (cm)	WEIGHT (kg)	BSA (m^2)	BMI (kg/m^2)	SEX M/F	RACE	EM/PM	DOSE (mg)	DOSE (mg/kg)
6 - 7 yo	6	6	6	6	6		W/B/A/O		6	6
	7.25 ± 0.6 (8.7) 6.3 - 7.9 [7.35]	124.6 ± 7.6 (6.1) 111.8 - 133.4 [125.75]	27.6 ± 7.9 (28.7) 17.3 - 41 [27.5]	0.97 ± 0.2 (16.9) 0.73 - 1.22 [0.99]	17.5 ± 3.7 (21.1) 13.8 - 24.3 [16.6]	5/1	2/4/0/0	6/0	43.75 ± 15.3 (35.0) 37.5 - 75 [37.5]	1.61 ± 0.3 (21.6) 1.27 - 2.17 [1.51]
8 - 11	6	6	6	6	6				6	6
	10.1 ± 1.2 (11.9) 8.5 - 11.4 [10.4]	140.95 ± 12.8 (9.1) 127 - 160 [141.6]	40.5 ± 12.7 (31.4) 26.3 - 56.8 [38.6]	1.25 ± 0.3 (20.3) 0.96 - 1.59 [1.23]	19.9 ± 3.1 (15.5) 16.3 - 24.1 [19.75]	6/0	6/0/0/0	5/1	56.25 ± 20.5 (36.5) 37.5 - 75 [56.25]	1.38 ± 0.2 (14.6) 1.12 - 1.72 [1.365]
12 - 17	6	6	6	6	6				6	6
	13.4 ± 0.9 (6.5) 12.2 - 14.2 [13.75]	161.0 ± 6.9 (4.3) 154 - 173 [160]	49.1 ± 8.3 (16.9) 39 - 60 [47.7]	1.48 ± 0.2 (10.6) 1.29 - 1.7 [1.46]	18.8 ± 1.8 (9.6) 16.4 - 21.3 [18.65]	5/1	6/0/0/0	5/1	68.75 ± 15.3 (22.3) 37.5 - 75 [75]	1.4 ± 0.3 (20.8) 0.96 - 1.76 [1.4]

a Values are Mean ± SD (CV) Range and [Median]

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