sNDA's 20-151, SE5-024; 20-699, SE5-030: Effexor (venlafaxine HCl) Tablets and Effexor XR (venlafaxine HCl) Extended-Release Capsules

NDA: 20-151
SUPPLEMENT: SE5-024
DRUG: Effexor (venlafaxine HCl) Tablets
NDA: 20-699
DRUG: Effexor XR (venlafaxine HCl) Extended-Release Capsules
SUPPLEMENT: SE5-030

SPONSOR: Wyeth-Ayerst Laboratories

MATERIAL SUBMITTED: Pediatric Exclusivity Supplement(s)

DATE SUBMITTED: 09/25/02

PDUFA DUE DATE: 03/26/03

REVIEWER: Glenn B. Mannheim, M.D.

CLINICAL REVIEW

Executive Summary Section

NDA: 20-151
SUPPLEMENT: SE5-024
DRUG: Effexor (venlafaxine HCl) Tablets
NDA: 20-699
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Executive Summary

I. Recommendations

A. Recommendation on Approvability

I recommend "non approvable" action(s) for the following indication(s):

1. Venlafaxine XR in the treatment of pediatric subjects with Major Depressive Disorder (MDD);
2. and Venlafaxine XR in the treatment of pediatric subjects with Generalized Anxiety Disorder (GAD).

Basis for Non-Approvable Action(s):

1. Failure of Venlafaxine XR to show statistical superiority over placebo in the treatment of pediatric subjects with MDD in two (2), phase III, parallel group, double blind, placebo controlled, flexible dose studies.

2. Failure of Venlafaxine XR to show statistical superiority over placebo in the treatment of pediatric subjects with GAD in one of two (2), phase III, parallel group, double blind, placebo controlled, flexible dose studies.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The following clinical trials were conducted:

Pediatric Pharmacokinetics:
Studies: 0600A-126-US (126)
0600B1-169-US (169)

Study 126 used venlafaxine immediate release (IR) in a 2 week, multiple dose (1 or 2 mg/kg day) pharmacokinetic study, followed by a 6 week, double blind study in 6-16 year olds with conduct disorder. This was followed by a 2 year open label safety and preliminary efficacy study.

Study 169 was a single site, open label, single dose study (0.96-2.17 mg/kg)evaluating the pharmacokinetics of venlafaxine extended release (ER) in 6, ADHD subjects, in each of the following 3 different age groups (6 to 7 years, 8 to 11 years, and 12 to 17 years).

Major Depressive Disorder (MDD):

Studies: 0600B1-382-US (382)
0600B1-394-US (394)

Two (2), 8 week, multi-center, parallel group, randomized, double blind, placebo controlled, flexible dose studies were conducted to evaluate the antidepressant efficacy and safety of venlafaxine XR (37.5 mg to 225 mg/day) versus placebo in the treatment of children and adolescents with major depressive disorder (161 [intent to treat], 103 [completers] in Study 382 and 193 [intent to treat, 143 [completers] in Study 394). This supplement includes safety information on a total of 182 pediatric subjects exposed to venlafaxine ER (99 Children and 78 adolescents).

Study: 0600B1-395-US (395): Longer-Term Safety Trial

One (1), 6 month, multi-center, open label study was conducted to evaluate the safety, efficacy, and clinical acceptability of Venlafaxine XR (37.5 mg to 225 mg/day) during long-term treatment in children and adolescent outpatients with major depressive disorder (85 [intent to treat], 36 [completers]). The open label study (395) in MDD provided 86 subjects who received venlafaxine ER for up to 6 months.

Hence, for MDD (382, 394 and 395) a total of 268 subjects participated in these three studies and received at least 1 dose of venlafaxine ER. The total exposure to venlafaxine ER in the pediatric MDD trials was 57 patient exposure years.

Generalized Anxiety Disorder (GAD):

Studies: 0600B2-396-US (396)
0600B2-397-US (397)

Two (2), 8 week, multi-center, parallel group, randomized, double blind, placebo controlled, flexible dose studies were conducted to evaluate the anxiolytic efficacy and safety of venlafaxine XR (37.5 mg to 225 mg/day) versus placebo in the treatment of children and adolescents with generalized anxiety disorder (160 [intent to treat], 130[completers] in Study 396 and 153 [intent to treat], 112 [completers] in Study 397). This supplement includes safety information on a total of 157 pediatric subjects exposed to venlafaxine ER (85 children and 72 adolescents). The total exposure to venlafaxine ER in the pediatric GAD trials was 24 patient exposure years.

B. Efficacy

The results for the two efficacy trials and open label safety study in MDD, and for the two efficacy trials in GAD are summarized under their respective headers (indications)below.

Major Depressive Disorder:

For Studies 382 and 394, the primary efficacy variable was the change from baseline in the total score of the Childhood Depression Rating Scale, Revised (CDRS-R total score). There were no differences between venlafaxine ER and placebo at week eight (8) on therapy, or, the last-observation-carried-forward (LOCF) on-therapy evaluation, as measured by this endpoint (382: P=0.338; 394: P=0.386).

Generalized Anxiety Disorder:

For Studies 396 and 397, the primary efficacy was the last-observation-carried-forward (LOCF) week 8 on-therapy evaluations for the mean scores on the Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia GAD Subsection, 9 delineated items, total score (C-KIDDIE-SADS GAD). In study 396, improvement ($p = 0.09$) occurred in venlafaxine ER treated subjects compared to placebo at week 8 of treatment on this efficacy measure. In study 397, venlafaxine ER showed a statistical difference over placebo at week 8 ($p < 0.001$) on this same efficacy measure based on the LOCF dataset. The secondary efficacy variables were the total scores on the C-KIDDIE- SADS GAD, Complete, Severity Component (5 delineated items) and Impairment Component (4 delineated items), the total score on the Pediatric Anxiety Rating Scale (PARS), the total score on the Hamilton Rating Scale for Anxiety (HAM-A), the

total scores for parent and for patient on the Self Report for Childhood Anxiety Related Disorder (SCARED) and the Clinical Global Impression Scale for Severity and Improvement (CGI-S and CGI-I). In study 397, venlafaxine ER showed a statistical difference compared to placebo on all the secondary efficacy endpoints: C- KIDDIE- SADS GAD Impairment (P=0.002), C- KIDDIE-SADS GAD Complete Total (P=0.001), PARS (P<0.001), HAM- A Total (P=0.003), CGI-S (P<0.001), CGI- I (P<0.001), and the SCARED Parent (P=0.007) and Patient Total (P=0.002). In study 396, venlafaxine ER showed a statistical difference compared to placebo only on the CGI-S (P=0.038) and CGI-I (P=0.018).

C. Safety

The safety profile of venlafaxine ER in children and adolescents was comparable to that in adults. Anorexia had an incidence of 5 % in venlafaxine ER- treated pediatric subjects, which was 2 times greater than placebo in both MDD and GAD studies. There were significant mean decreases in weight with venlafaxine ER treated pediatric subjects. The increase in height with venlafaxine ER was smaller than that with placebo in the pooled GAD studies. Therefore, venlafaxine ER may impact growth and development in children and adolescents. Total serum cholesterol showed a smaller increase from baseline in pediatric compared to adult MDD and a higher increase from baseline in pediatric GAD compared to adult GAD. Mean increases in pulse rate and statistically significant inquiries in ECG heart rates occurred with venlafaxine ER compared with placebo, comparable to those observed in adults.

D. Dosing

No dosing recommendations can be made based upon these data, since efficacy in the pediatric populations for MDD and GAD were not established.

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation I (OCPB/DPE-1) notes in their review of the two pharmacokinetic studies that exposure to venlafaxine is slightly lower in adolescents 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 pre-adolescents. 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".

E. Special Populations

This supplement is limited to data in the pediatric population which includes children (ages 7-12) and adolescents (ages 13-17).

In study 396, venlafaxine ER had a statistically significant treatment effect on the reduction of C-KIDDIE-SADS GAD (9 delineated items)in the white race group (p=0.01) but not in the nonwhite race group (p=0.31). Similarly, in study 397, a highly significant treatment effect occurred in the white race group (p=0.003) but not in the nonwhite group (p=0.21). In study 397, this was related to the low sample size, given that the treatment effect in the nonwhite group was in the same direction and of a similar magnitude. Pooling of the data for 396 and 397 (n=233 whites, 76 non-whites) showed that a statistical treatment effect on the reduction of C-KIDDIE-SADs (9 delineated items)occurred in the white group (p=.001) but not in the non-white group (p=0.83). No such racial differences between whites and non-whites were present in individual or pooled data in study 382 or 394 looking at changes in CDRS-R total score in MDD.

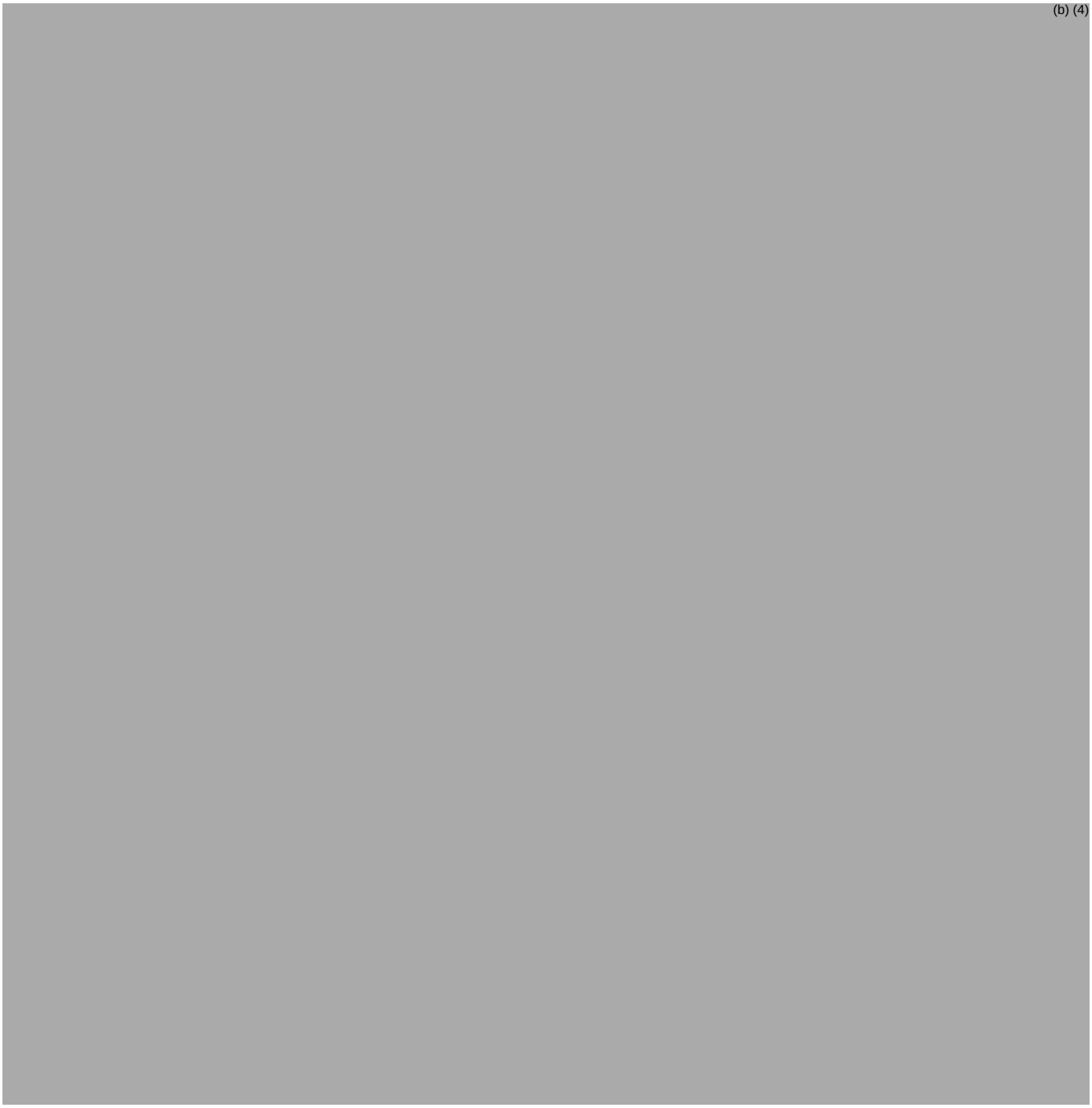
Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

The sponsor is not seeking an indication for pediatric MDD, but is seeking an indication for pediatric GAD. WAL's proposed labeling is:

(b) (4)


(b) (4)

B. State of Armamentarium for Indication(s)

Prozac (fluoxetine HCl) was recently approved (1/3/2003) for the treatment of major depressive disorder and OCD. Side effects associated with its use include manic reaction (2.6 %), a decrease in weight gain and a decrease in growth (1.1 cm less in height and 1.1 kg less in weight compared to placebo after 19 weeks).

No drugs are currently approved for the treatment of GAD in children.

Effexor IR is indicated for the treatment of depression in adults and Effexor XR is indicated for the treatment of depression and generalized anxiety disorder in adults.

C. Important Milestones in Product Development

On 12/30/1998, Wyeth-Ayerst Laboratories (WAL) submitted a Pediatric Study Request (PPSR) for Effexor XR (37.5 mg, 75 mg, 100 mg, and 150 mg) Capsules requesting that FDA provide a written request for pediatric trials using venlafaxine so that they could obtain the 6-month pediatric exclusivity extension under FDAMA (1997). A written request was issued by the FDA on 04/28/1999 and amended on 07/07/2000 and 12/18/2001. The FDA request asked for two (2) adequate, well controlled efficacy and safety studies in children (7-11 yrs) and adolescents (12-17 yrs) in MDD and two, similar studies, in GAD; PK and safety studies in the appropriate age groups; validated symptom rating scale specific to the disorder and sensitive to drug effects and a global measure; and a long term safety study at clinically effective doses for a sufficient duration of time. Amendments to the request changed the ages of children (ages 7-12) and adolescents (ages 13-17); required that the same venlafaxine formulation be used for PK and efficacy studies and that sufficient number of subjects be evaluated for different age ranges; and gave an additional 6 months extension for the initial 3-year timeframe for completion of the study to 11/28/2002. A meeting between FDA and WAL took place on 08/08/2001 to discuss the content and formatting of the sNDA's for pediatric MDD & GAD. The studies were submitted to the Agency on 09/25/2002. The pediatric exclusivity board convened on 12/02/2002 and determined that Wyeth adequately met the terms of the Agency's pediatric written request letter, and therefore, allowed for Wyeth to receive an additional 6 months of patent protection for all venlafaxine products.

D. Important Issues with Pharmacologically Related Agents

Venlafaxine IR has been associated with treatment emergent anorexia and weight loss, sustained increases in blood pressure, nervousness, anxiety and insomnia, and increases in serum cholesterol. Venlafaxine IR also has the potential for interaction with monoamine oxidase inhibitor's (MAOI) which may result in a range of outcomes ranging in tremor, seizures, a neuro-malignant like syndrome or death.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

1. The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation I (OCPB/DPE-1) notes in their review that the 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 pre-adolescents. 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."

2. The Division of Biometrics I (HFD-710) confirms the results reported by the sponsor in the LOCF analysis for the primary efficacy, C-KIDDIE-SADS GAD (9 delineated items) for Study 396 and 397 for GAD. A statistically significant reduction in C-KIDDIE-SADS GAD (9 delineated items) occurred in study 396 and 397 in white, but, not in non-white groups. In study 397 this may have been related to low sample size. Pooling of the data for 396 and 397 (n=233 whites, 76 non-whites) showed that a statistical treatment effect on the reduction of C-KIDDIE-SADs (9 delineated items)occurred in the white group (p=.001) but not in the non-white group (p=0.83). No such racial differences between whites and non-whites were present in individual or pooled data in study 382 or 394 looking at changes in CDRS-R total score in MDD.

3. The Good Clinical Practice Branch I & II (HFD-46/47),Division of Scientific Investigations, inspected 3 investigator sites for MDD and 3 investigator sites for GAD. Deficiencies in the

informed consent process, in source documentation and in enrolling subjects who should have been excluded occurred at one of the three sample sites in MDD (David Rosenberg, MD-Warren, Michigan. Data from this was to be excluded for study 382. No deficiencies were identified in the sites inspected for the GAD studies 396 and 397.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Two pediatric pharmacokinetic studies were conducted with venlafaxine. Study 0600A-126-US (126) was a multiple dose (1 or 2 mg/kg day) study of the steady-state pharmacokinetics of venlafaxine IR tablets after 14 days of dosing which was conducted in twenty-five, 6-16 year olds with conduct disorder. Study 0600B1-169-US (169) was a single dose study using venlafaxine ER capsules which evaluated the pharmacokinetics in 6, ADHD subjects, in each of the following 3 different age groups (6 to 7 years, 8 to 11 years, and 12 to 17 years). The purpose of this study was to evaluate if absorption of a sustained release product may be truncated in younger children as a possible consequence of a shorter gastrointestinal transit time.

In both studies pediatric subjects were grouped by age and tanner stage (i.e. tanner stage > 3 = adolescents).

A summary of the study designs is shown in Table 1.

Table1: 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

Plots of dose normalized AUC's versus age that are presented in the OCPB review demonstrated that exposures to venlafaxine and the active metabolite, O-desmethyl-venlafaxine (ODV), are lower in adolescents than in adults, when adjusted given the same

weight normalized dose, (e.g. mg/kg dose); plus, dose normalized AUC's are even lower in preadolescents and younger children.

Based upon these plots it appears that young preadolescent children may need a 2-4 fold higher dose on a mg/kg/basis as compared to adults. Adolescents may need only a higher slightly higher mg/kg/dose as compared to adults. As the average dose in adults is 2 mg/kg, an average dose of 4 – 8 mg/kg would be expected to be needed in children of various ages, and a dose of about 2.5 - 3 mg/kg is expected to be needed in adolescents. In contrast, average doses of 2.6 – 2.7 mg/kg were used in children < 50 kg in the various pediatric efficacy studies. Consequently, children weighing < 50 kg may have been under-dosed in these studies.

IV. Description of Clinical Data and Sources

A. Overall Data

The clinical data for these two supplements comes from two pharmacokinetic studies (126, 169), two controlled efficacy trials in MDD in children and adolescents (382, 394), one open label longer-term safety trial in MDD in children and adolescents (395), and two controlled efficacy trials in GAD in children and adolescents (396, 397).

B. Tables Listing the Clinical Trials

Tables 2.1 A and 3.1 A summarizes the two efficacy trials, each for MDD (382, 394)and for GAD (396, 397), and are included in the Appendix.

C. Postmarketing Experience

The sponsor reports that marketing authorization applications for venlafaxine and venlafaxine XR have been approved in 79 and 76 countries, respectively. The sponsor further states that they have not submitted any marketing authorization applications seeking approval for the use of venlafaxine XR in the treatment of MDD and GAD in pediatric subjects.

D. Literature Review

The sponsor performed a literature search of published papers and abstracts on pediatric subjects with MDD and, or, GAD relevant to venlafaxine. The sponsor states that after reviewing the world literature they found no issues that would adversely affect the conclusions about the safety of venlafaxine XR in pediatric subjects with MDD or GAD. Thirteen abstracts or, full

publications were included with these two supplements. These articles were reviewed by this reviewer and generally support the sponsor's statement regarding safety. One report[1] describes a child who developed unexplainable dystonia when venlafaxine was used with guanfacine in a 13-year-old with depression and ADHD. One abstract[2] describes the experiences of 14 cases of acute, accidental ingestion of venlafaxine in children, 15 mths-5.5 yrs, at a dose of 2.1-5.5 mg/kg, with one needing hospitalization because of lethargy. Another article[3] is not clearly relevant to pediatric MDD or GAD, albeit, indirectly.

V. Clinical Review Methods

A. How the Review was Conducted

The clinical review was divided into two general sections- efficacy and safety review. The review of efficacy focused on the individual pivotal studies. There was no examination of pooled efficacy data. Safety data was examined starting from the integrated summary of safety (ISS).Serious adverse events, and adverse dropouts were reviewed for all studies relating to pediatric MDD and GAD. Data from controlled clinical trials of MDD and GAD were pooled, when appropriate, to explore common and drug related adverse events, treatment related changes in laboratory analytes, changes in ECG and vital signs, and other specific searches.

B. Overview of Materials Consulted in Review

The electronic version of this submission was used for the entire clinical process. The NDA application was generally complete. For the most part, the clinical review drew only from materials included in the NDA submission.

1 Chong Y, Harris R, Kim WJ Dystonia as a side effect of non- neuroleptics Journal of the American Academy of Child & Adolescent Psychiatry 1999; 38: 793- 795

2 Herrington LF, Gorman SE Pediatric ingestion of effexor (venlafaxine) Journal of Toxicology Clinical Toxicology 1996; 34: 558- 559

3 Hollander E, Kaplan A, Cartwright C, Reichman D Venlafaxine in children, adolescents, and young adults with autism spectrum disorders: an open retrospective clinical report Journal of Child Neurology 2000; 15: 132- 135

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The submission was checked for internal consistency. Various narrative summaries were checked against the table listings to help ensure the accuracy of some of the safety data. The Division of Scientific Investigations (DSI) was consulted and sample site visits were made by them.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Trials were conducted in accordance with Good Clinical Practice Guidelines (GCP).

E. Evaluation of Financial Disclosure

The sponsor disclosed that the following principal investigators for the identified studies received in excess of $ 25,000, and that the financial assets that they received were not likely to have influenced the medical assessments of the efficacy and safety endpoint of these studies:

1. (b) (6): (b) (4)
   - For honoraria, travel, and participation in the investigators meeting

2. (b) (6): (b) (4)
   - For participation at the investigators meeting

3. (b) (6): (b) (4)
   - For being a visiting professor, for honoraria, travel and for participation at the investigators meeting

4. And, (b) (6), (b) (4)
   - For travel and for participation at the investigators meeting.

The small sample of subjects at each of the investigator's sites and the fact that these were double-blind trials suggest that the integrity of these studies was not adversely influenced by the financial conflicts.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

(b) (4)

[redacted]

B. General Approach to Review of the Efficacy of the Drug

The review of clinical efficacy of venlafaxine ER in the treatment of MDD in children and adolescents focused on the two (2) parallel group, randomized, double blind, placebo controlled, flexible dose studies (382, 394) on an individual basis.

The review of clinical efficacy of venlafaxine ER in the treatment of GAD in children and adolescents focused on the two (2) parallel group, randomized, double blind, placebo controlled, flexible dose studies (396, 397) on an individual basis.

C. Detailed Review of Trials by Indication

Major Depressive Disorder (MDD) Studies: 0600B1-382-US (382)and 0600B1-394-US (394)

Study: 0600B1-382-US (382): This study was conducted over the 3.11 year period from 10/97-09/00, by the investigators/sites identified in the Appendix.

Objective(s): The purpose for this study was to compare the antidepressant efficacy and safety of venlafaxine extended release (ER) to placebo in children and adolescents with MDD.

Population: The subjects were to be healthy, capsule swallowing, outpatient children (7-12 years) and adolescents (13-17 years)

who met DSM- IV and KIDDIE-SADS-PL[4] criteria for MDD, and whose symptoms were present for ≥ 1 month. Subjects were to have a CDRS-R score ≥ 40 at prestudy and study day –1 visits, and must not have had a > 30% decrease in there CDRS-R score between prestudy and study day –1. In addition, the subjects were to have a CGI-S ≥ 4 score at day –1.

Design: Following 14 ± 3 day single-blind placebo lead-in period, 166 subjects were randomly assigned to venlafaxine ER capsules or placebo, stratified by age, with flexible dosing by body weight(37.5 mg to 225 mg/day), for up to 8 weeks, followed by a taper period of up to 14 days. Concomitant use of psycho-pharmacological drugs (e.g. antipsychotics, anxiolytics, other antidepressants, lithium, stimulants and sedative hypnotics) was prohibited.

Of the 166 subjects who entered the double blind period, 165 were analyzed for safety and 161 for efficacy (intent to treat), with 103 subjects ending up completing the study. The treatment groups were comparable in demographic and baseline character-istics(weight, height, duration of current episode, CDRS-R, Ham-D total, MADRS Total and CGI-S), except for the fact that there were more females in the placebo group and more males in the drug group.

TABLE 8.2A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR ALL PATIENTS

Characteristic	Placebo (n = 85)	Venlafaxine ER (n = 80)	p-Value	Statistical Test[a]
Age (years)	(n = 84)	(n = 79)	0.829	t
Mean	12.2	12.3		
SD	2.6	2.6		
Range	7-17	8-17		
Children (ages 7-12), n (%)	47 (55)	42 (53)		
Adolescents (ages 13-17), n (%)	38 (45)	38 (48)		
Sex, n (%)			0.186	C
Female	47 (55.3)	36 (45.0)		
Male	38 (44.7)	44 (55.0)		
Ethnic origin, n (%)			0.777	C
White	75 (88.2)	70 (87.5)		
Black	7 (8.2)	6 (7.5)		
Hispanic	3 (3.5)	3 (3.8)		
Other	0	1 (1.3)		

Assessments: Screening assessments were to include a medical and psychiatric history, physical exam, clinical laboratories, ECG, HAM-D, CDRS-R, MADRS, KIDDIE SADS, and DSM-IV Criteria for MDD. The primary efficacy measure was the CDRS-R total score and the secondary efficacy measures were HAM-D total + depressed mood

[4]Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version

item scores, MADRS[5] total score and CGI-S. Safety monitoring assessment included physical examinations, vital signs, height and weight, ECG's, clinical laboratories and recording of adverse events. CDRS- R, CGI- S scores, HAM- D total and depressed mood items, MADRS were evaluated at prestudy, baseline and study days 4, 7, 14, 21, 28, 42 and 56.

Analysis Plan: The primary outcome was the change from baseline on the CDRS-R total score at week 8 of therapy, or the last observation carried forward (LOCF) in the venlafaxine ER group compared to the placebo group. An LOCF analysis was performed at all other time points with the secondary efficacy data. The CDRS-R, HAM-D total and depressed mood item, MADRS total, and CGI-S item scores were analyzed using an analysis of covariance. The CGI-I item score was analyzed using an analysis of variance (ANOVA) with treatment and investigator as factors. A responder analysis was also performed, where on the CDRS-R scale, subjects whose total scores decreased by 35% or more from baseline were considered responders; and where, on the HAM-D and MADRS scales, subjects whose total scores decreased by 50% or more from baseline were considered responders.

Study Subjects: Eighty (80) subjects received at least a single dose of venlafaxine ER at a mean daily dose of 2.4-2.7 mg/kg for 11.01 patient exposure years. Eight-five (85) subjects received a single dose of placebo for 11.73 patient exposure years. A total of 62 (38%) subjects discontinued from the study prematurely. The most frequent reasons for discontinuation in the venlafaxine ER group were "failed to return" and "adverse events" and in the placebo group were "failed to return" and "lack of efficacy. Adverse events were the primary or a secondary cause for discontinuation of on-therapy treatment for 10 (13%) of the venlafaxine ER-treated patients and 4 (5%) patients in the placebo group. The adverse events that most frequently (.2%) caused discontinuation of treatment in the venlafaxine ER group were manic reaction and suicidal ideation, and which are identified in sponsor's Table 10.3.3A which is included in the Appendix. Forty-one (41, 51%) of the 80 venlafaxine ER-treated patients had an adverse event resulting in a dose reduction or administration of concomitant therapy compared to fifty-two (52, 61%) of the 85 placebo-treated patients who had an adverse event resulting in a dose reduction or administration of concomitant therapy.

[5] Montgomery-Asberg Depression Rating Scale

Results: There was no difference between the venlafaxine ER and the placebo groups on the primary and secondary efficacy parameters [primary: CDRS-R total (P=0.338); secondary: HAM-D Total (P=0.737), HAM-D Depressed Mood Item (P=0.544), MADRS Total (P=0.405),CGI-S (P=0.792) and CGI-I (P=0.692)]. Subjects in the adolescent subpopulation did slightly better on venlafaxine ER than on placebo, but, the difference was not statistically significant.

Conclusion(s): This study showed that in pediatric age groups, venlafaxine ER was not statistically superior to placebo on the primary and secondary efficacy measures chosen. Greater, but not statistically significant, improvement occurred in adolescent compared to children subpopulation(s).

Study: 0600B1-394-US (394): This study was conducted over 1 year between 08/00-08/01, by the investigators/sites identified in the Appendix.

Objective(s): The purpose for this study was to compare the antidepressant efficacy and safety of venlafaxine extended release (ER) to placebo in children and adolescents with MDD.

Population: The subjects were to be healthy, capsule swallowing, outpatient children (7-12 years) and adolescents (13-17 years) who met DSM-IV and KIDDIE-SADS-PL criteria for MDD, and whose symptoms were present for ≥ 1 month. Subjects were to have a CDRS-R score ≥ 40 at prestudy and study day –1 visits, and must not have had a > 30% decrease in there CDRS-R score between prestudy and study day –1. In addition, the subjects were to have a CGI-S ≥ 4 score at day –1.

Design: Following 7 ± 3 day single-blind placebo lead-in period, 201 subjects were randomly assigned to venlafaxine ER capsules or placebo, stratified by age, with flexible dosing by body weight (37.5 mg to 225 mg/day), for up to 8 weeks, followed by a taper period of up to 14 days. Concomitant use of psycho-pharmacological drugs (e.g. antipsychotics, anxiolytics, other antidepressants, lithium, stimulants and sedative hypnotics) was prohibited.

Of the 201 subjects who entered the double blind period, 196 were analyzed for safety and 193 for efficacy (intent to treat), with 148 subjects ending up completing the study. The treatment groups were comparable in demographic and baseline characteristics (weight, height, duration of current episode, CDRS-R, Ham-D total, MADRS Total and CGI-S).

TABLE 8.2A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR PATIENTS IN THE SAFETY POPULATION

Characteristic	Placebo (n = 94)	Venlafaxine ER (n = 102)	p-Value	Statistical Test[a]
Age, years			0.778	t
Mean	12.1	12.2		
SD	2.8	2.6		
Range	7-17	7-17		
Children, n (%)	54 (57)	57 (56)		
Adolescents, n (%)	40 (43)	45 (44)		
Sex, n (%)			0.816	c
Female	39 (41)	44 (43)		
Male	55 (59)	58 (57)		
Ethnic origin, n (%)			0.088	c
Black	10 (11)	15 (15)		
Hispanic	11 (12)	13 (13)		
White	71 (76)	64 (63)		
Other	2 (2)	10 (10)		

Assessments: Screening assessments were to include a medical and psychiatric history, physical exam, clinical laboratories, ECG, HAM-D, CDRS-R, MADRS, KIDDIE SADS, and DSM-IV Criteria for MDD. The primary efficacy measure was the CDRS-R total score and the secondary efficacy measures were HAM-D total and depressed mood item scores, MADRS[6] total score and CGI-S. Safety monitoring assessment included physical examinations, vital signs, height and weight, ECG's, clinical laboratories and recording of adverse events. CDRS-R, CGI-S scores, HAM-D total and depressed mood items, MADRS were evaluated at prestudy, baseline and study days 4, 7, 14, 21, 28, 42 and 56.

Analysis Plan: The primary outcome was the change from baseline on the CDRS-R total score at week 8 of therapy, or the last observation carried forward (LOCF) in the venlafaxine ER group compared to the placebo group. An LOCF analysis was performed at all other time points with the secondary efficacy data. The CDRS-R, HAM-D total and depressed mood item, MADRS total, and CGI-S item scores were analyzed using an analysis of covariance. The CGI-I item score was analyzed using an analysis of variance (ANOVA) with treatment and investigator as factors. A responder analysis was also performed, where on the CDRS-R scale, subjects whose total scores decreased by 35% or more from baseline were considered responders; and where, on the HAM-D and MADRS scales, subjects whose total scores decreased by 50% or more from baseline were considered responders.

[6] Montgomery-Asberg Depression Rating Scale

Study Subjects: One hundred and ninety six subjects (196; venlafaxine ER: 102, placebo: 94) received at least one dose of study medication with the mean daily dose of venlafaxine ER being 2.4-2.6 mg/kg for 15.95 patient exposure years (vs. 15.47 patient exposure years for placebo). Of the 196 patients who received study medication, 45 (23%) subjects (venlafaxine ER, n= 28; placebo: n=17) discontinued treatment prematurely. For the venlafaxine ER group, "adverse event (n=8)" "failed to return (n=8)," and "unsatisfactory response (n=8)" were the most frequent primary reasons for discontinuation. "Other event (placebo, n=5; venlafaxine ER, n=3)" was the most frequent primary reason for discontinuation in the placebo group. The adverse events that most frequently (≥ 2%) caused discontinuation of treatment in the venlafaxine group were hostility (2%) and suicidal ideation (2%). Eighty-nine (89, 87%) of the 102 venlafaxine ER patients and 77 (82%) of the 94 placebo patients received some type of concomitant therapy. The most frequently used concomitant medications were analgesics/antipyretics, antihistamines, and nonsteroidal anti-inflammatory drugs.

Results: There was no difference between the venlafaxine ER and the placebo groups on the primary and secondary efficacy parameters [primary: CDRS-R total (P=0.386); secondary: HAM-D Total (P=0.567), HAM-D Depressed Mood Item (P=0.211), MADRS Total (P=0.214),CGI-S (P=0.339) and CGI-I (P=0.261)].

Conclusion(s): This study showed that in pediatric age groups, venlafaxine ER was not statistically superior to placebo on the primary and secondary efficacy measures chosen.

Generalized Anxiety Disorder (GAD) Studies: 0600B2-396-US (396)and 0600B2-397-US (397)

Study: 0600B2-396-US (396): This study was conducted over 13 months between 08/00-09/01, by the investigators/sites identified in the Appendix.

Objective(s): The purpose for this study was to compare the anxiolytic efficacy and safety of venlafaxine extended release (ER) with placebo in children and adolescents with GAD.

Population: The subjects were to be healthy, capsule swallowing, outpatient children (6-11 years) and adolescents (12-17 years) who met DSM-IV[7] and C-KIDDIE-SADS GAD[8] criteria for GAD, and

[7] Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition.

whose anxiety symptoms were present for ≥ 6 months. Subjects were to have a Severity Component[9], 5 item, CKIDDIE-SADS GAD score ≥ 20 at prestudy screen and SD - 1 (baseline); a Severity Component[10], 3-items, CKIDDIE-SADS GAD score = 4 at prestudy screen and SD - 1 (baseline); a Severity Component[11], 2 items, CKIDDIE-SADS GAD score = 4 at prestudy screen and SD - 1 (baseline); a Impairment Component[12], 4-item, C-KIDDIE-SADS GAD score = 7 at prestudy screen and SD -1 (baseline); a Impairment Component[13], 1 item, CKIDDIE-SADS GAD score ≥ 4 at prestudy screen and SD - 1 (baseline); a CDRS-R[14] score < 45 prestudy and SD -1 (baseline); and a CGI-S[15] score = 4 at prestudy screen and SD- 1 (baseline).

Design: Following a 7 ± 3 day single-blind placebo lead in period, 164 subjects were randomly assigned to venlafaxine ER capsules or placebo, with flexible dosing (37.5 mg to 225 mg/day), for up to 8 weeks, followed by a taper period of up to 14 days. Concomitant use of psycho-pharmacological drugs (e.g. antipsychotics, anxiolytics, other antidepressants, lithium, stimulants and sedative hypnotics) was prohibited.

Assessments: Screening assessments were to include a medical and psychiatric history, recording of prior medications, physical exam, VS, HT, WT, clinical laboratories, serum beta-HCG for females, ECG, C-KIDDIE-SADS GAD (Complete), CGI-S, CDRS-R, CKIDDIE-SADS PL [Anxiety (excluding GAD) and Affective Disorder Supplements], and the DSM-IV Criteria for GAD. The primary efficacy measure was the LOCF or week 8 on-therapy evaluation of the C-KIDDIE-SADS GAD[16] (9 delineated items). The secondary efficacy measures were the total scores on the C-KIDDIE-SADS GAD, Complete, Severity Component (5 delineated items) and Impairment Component (4 delineated items), the total score on the PARS[17], the total score on the HAM-A[18], the Parent and Patient total scores on the SCARED[19], the CGI-S and CGI-I, and

[8] Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia GAD Subsection
[9] 5 Severity questions in the 9 delineated items
[10] Anxiety + worry, difficulty controlling the worry + severity of associated symptoms
[11] Frequency of anxiety and worry during the average week and frequency of associated symptoms during the average week.
[12] 4 Impairment questions in the 9 delineated items
[13] Global impairment in functioning
[14] Childhood Depression Rating Scale-Revised
[15] Clinical Global Impressions - Severity of Illness
[16] C-Kiddie SADS GAD, a subset of 9 items, was chosen as the primary because it correlates with DSM-IV GAD Diagnostic Criteria for Children; 5 items comprise the severity component + 4 items comprise the impairment component; given weekly to identify changes in the severity and impairment of the anxiety symptoms
[17] Pediatric Anxiety Rating Scale
[18] Hamilton Rating Scale for Anxiety
[19] Self Report for Childhood Anxiety Related Disorder

the C-KIDDIE-SADS GAD (9 delineated items), PARS and CGI-I scores to assess responder status. Safety monitoring assessment included physical examinations, vital signs, height and weight, ECG's, clinical laboratories and recording of adverse events. The efficacy measurements were made at the following time intervals: C-KIDDIE-SADS GAD (complete) at prestudy, baseline (day-1), and study days 28 and 56; C-KIDDIE-SADS GAD (9 delineated items) on study days 7, 14, 21, 42, and 49; PARS at baseline (day-1) and study days 7, 14, 21, 28, 42, 49, and 56; HAM-A at baseline (day -1) and study days 28 and 56; SCARED parent and patient forms at baseline (day-1) and study days 28 and 56; CGI (Severity only)at prestudy visit and baseline (day -1); and the CGI (Severity and Improvement) at study days 7, 14, 21, 28, 42, 49, and 56.

Analysis Plan: The primary outcome measures were the change from baseline on the week 8 last-observation-carried-forward (LOCF) on-therapy evaluation. In addition to an LOCF analysis, an analysis of the observed data at each time point was performed using a parametric 2-way analysis of covariance (ANCOVA) with treatment and investigator as factors and the associated baseline as the covariate. The observed data and LOCF data analyses were applied to the primary and secondary variables. Changes from baseline for the primary and secondary efficacy variables (e.g., C-KIDDIE-SADS GAD [9 delineated items, severity component, impairment component, and complete], PARS, HAM-A, CGI-S, and SCARED scales), were analyzed at each time point.

Patient Disposition: Of the 164 subjects who entered the double blind period, 164 were analyzed for safety and 160 for efficacy (intent to treat), with 129 subjects ending up completing the study. The primary reasons for 34 (21%) subjects discontinuing the study prematurely are identified in Table 8.1.1A below provided by the sponsor in Final Study Report CSR-44723. "Failed to return" was the most frequent primary reason for discontinuation. Adverse events were the primary or a secondary cause for discontinuation of double- blind treatment for 3 (4%) subjects in the venlafaxine ER treated group and for 2 (2%) subjects in the placebo group.

The disposition over time of all the subjects who entered the study is shown in Table 8.1C. taken from CSR-44723. The number who completed (C) and the number who discontinued (D) are shown by time period.

TABLE 8.1C. PATIENT STATUS OVER TIME: NUMBER (%) OF PATIENTS – ON THERAPY

	Placebo (n = 84)		Venlafaxine ER (n = 80)	
Time Period (days)[a]	C[b,c]	D[b]	C[b]	D
1 to 7	84	4	80	1
8 to 14	80	2	79	3
15 to 21	78	2	76	2
22 to 28	76	2	74	2
29 to 35	74	1	72	4
36 to 42	72	1	68	1
43 to 49	72	4	67	3
50 to 56	66	0	63	2
>56	28	0	38	4

a: Does not include taper period.
b: C = the number of patients who completed the indicated treatment period. D = the number of patients who discontinued by end of each treatment period.
c: If patients completed early or missed a dose, they are not counted in the C column.
3-4IT 22 Mar 2002

The treatment groups were comparable in demographic and baseline characteristics (height, duration of current episode, C-KIDDIE-SADS GAD (9 delineated items), C-KIDDIE-SADS (Complete), C-KIDDIE-SADS (Impairment), C-KIDDIE-SADS (Severity), PARS, HAM-A, SCARED parent, SCARED patient and the CGI-severity. Statistically significant baseline differences in the distribution of sexes was present. More male subjects were present in the venlafaxine ER than in the placebo groups, however, the mean body weights were comparable between the two groups (venlafaxine ER: 48.7 kg; placebo: 51.5 kg. Baseline characteristics of age, sex and ethnic origin are identified in Table 9.2.1A provided by the sponsor in CSR-44723.

TABLE 9.2.1A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS INTENT-TO-TREAT POPULATION

Characteristic	Placebo (n = 82)	Venlafaxine ER (n = 78)	p-Value/ Statistical Test[a]
Age, years			0.566[b]
Mean	11.1	11.4	
SD[b]	2.6	3.2	
Range	6.0-17.0	6.0-17.0	
Sex, n (%)			
Female	46 (56)	27 (35)	0.006[c]
Male	36 (44)	51 (65)	
Ethnic origin, n (%)			
Arabic	1 (1)	0 (0)	
Asian	0 (0)	1 (1)	
Black	7 (9)	7 (9)	0.674[c]
Hispanic	14 (17)	13 (17)	
Native American	0 (0)	1 (1)	
Other	1 (1)	0 (0)	
White	59 (72)	56 (72)	

The dose information for all subjects who were exposed to at least one dose of venlafaxine ER (n = 80) is summarized in Table 10.1B. After the initial 28-day titration period, mean daily doses of venlafaxine ER per kilogram of body weight were 2.6 to 2.7 mg.

TABLE 10.1B. MEAN DAILY DOSE BY TIME INTERVAL

Time Interval (days)	n	Daily Dose Mean ± SD (mg/kg)
On-therapy[a]		
0 - 7	80	0.9 ± 0.3
8 - 14	79	1.4 ± 0.5
15 - 21	76	1.9 ± 0.6
22 - 28	74	2.1 ± 0.6
29 - 35	72	2.6 ± 0.8
36 - 42	68	2.8 ± 0.7
43 - 49	67	2.8 ± 0.7
50 - 56	63	2.7 ± 0.8
>56[b]	38	2.6 ± 0.8
Taper	57	1.7 ± 0.5

a: On-therapy period excludes taper doses.
b: Patients who had their week 8 visit outside the scheduled window for this visit.
4-2ALL, 22 Mar 2002

Results: The LOCF analyses for the mean scores on C-KIDDIE-SADS GAD (9 delineated items) total score showed marginal improvement (p=0.06) in venlafaxine ER treated subjects compared to placebo at week 8 of treatment. Treatment with venlafaxine ER was significantly ($p < 0.05$) better than treatment with placebo according to the results of the LOCF analyses for the mean scores on the CKIDDIE-SADS GAD Severity component at weeks 4 and 8, the CGI-S at weeks 2, 3, and 8, the CGI-I at weeks 3, 6, 7, and 8, and the SCARED patient at week 4. The observed cases analyses revealed a significant benefit for drug at Week 8 on the C-KIDDIE-SADS GAD Severity subscale ($p = 0.05$) and at Week 3 on the CGI-S ($p < 0.03$) and CGI-I ($p < 0.03$). Based on the CGI-I score, significantly more subjects on drug were reported to have been " much improved" or " very much improved" (e.g., responders) at weeks 6,7, and 8 (LOCF) compared with subjects in the placebo group ($p = 0.008$, 0.010, and 0.008). In the observed -cases analysis (CGI-I score), significantly drug subjects responded at week 8 compared to placebo($p = 0.044$). Table 9.41A, located in the Appendix, compares the LOCF analysis between treatment groups for the intent to treat subjects, and was provided by the sponsor in Final Study Report CSR-44723.

Conclusion(s): The results of the LOCF analyses of the primary efficacy variable, C-KIDDIE-SADS GAD (9 delineated items) scores, showed that subjects treated with venlafaxine ER were not significantly better than subjects treated with a placebo at the primary time point, week 8 ($p = 0.06$).

Study: 0600B2-397-US (397): This study was conducted over 16 months between 04/00-08/01, by the investigators/sites identified in the Appendix.

Objective(s): The purpose for this study was to compare the anxiolytic efficacy and safety of venlafaxine extended release (ER) with placebo in children and adolescents with GAD.

Population: The subjects were to be healthy, capsule swallowing, outpatient children (6-11 years) and adolescents (12-17 years) who met DSM-IV and C-KIDDIE-SADS GAD criteria for GAD, and whose anxiety symptoms were present for ≥ 6 months. Subjects were to have a Severity Component, 5 item, CKIDDIE-SADS GAD score ≥ 20 at prestudy screen and SD-1 (baseline); a Severity Component, 3-items, CKIDDIE-SADS GAD score = 4 at prestudy screen and SD-1 (baseline); a Severity Component, 2 items, CKIDDIE-SADS GAD score = 4 at prestudy screen and SD - 1 (baseline); a Impairment Component, 4- item, C-KIDDIE-SADS GAD score = 7 at prestudy screen and SD - 1 (baseline); a Impairment Component, 1 item, CKIDDIE-SADS GAD score ≥ 4 at prestudy screen and SD-1 (baseline); a CDRS-R score < 45 prestudy and SD-1 (baseline); and a CGI-S score = 4 at prestudy screen and SD-1 (baseline).

Design: Following a 7 ± 3 day single-blind placebo lead in period, 158 subjects were randomly assigned to venlafaxine ER capsules or placebo, with flexible dosing (37.5 mg to 225 mg/day), for up to 8 weeks, followed by a taper period of up to 14 days. Concomitant use of psycho-pharmacological drugs (e.g. antipsychotics, anxiolytics, other antidepressants, lithium, stimulants and sedative hypnotics) was prohibited.

Assessments: Screening assessments were to include a medical and psychiatric history, recording of prior medications, physical exam, VS, HT, WT, clinical laboratories, serum beta-HCG for females, ECG, C-KIDDIE-SADS GAD (Complete), CGI-S, CDRS-R, CKIDDIE-SADS PL [Anxiety (excluding GAD) and Affective Disorder Supplements], and the DSM-IV Criteria for GAD. The primary efficacy measure was the LOCF or week 8 on-therapy evaluation of the C-KIDDIE-SADS GAD (9 delineated items). The secondary efficacy measures were the total scores on the C-KIDDIE-SADS GAD, Complete, Severity Component (5 delineated items) and Impairment Component (4 delineated items), the total score on the PARS, the total score on the HAM-A, the Parent and Patient total scores on the SCARED, the CGI-S and CGI-I, and the C-KIDDIE-SADS GAD (9 delineated items), PARS and CGI-I scores to assess responder status. Safety monitoring assessment included physical examinations, vital signs, height and weight, ECG's, clinical laboratories and recording of adverse events. The efficacy measurements were made at the following time intervals:

C-KIDDIE-SADS GAD (complete) at prestudy, baseline (day -1), and study days 28 and 56; C-KIDDIE-SADS GAD (9 delineated items) on study days 7, 14, 21, 42, and 49; PARS at baseline (day -1) and study days 7, 14, 21, 28, 42, 49, and 56; HAM-A at baseline (day -1) and study days 28 and 56; SCARED parent and patient forms at baseline (day -1) and study days 28 and 56; CGI (Severity only) at prestudy visit and baseline (day -1); and the CGI (Severity and Improvement) at study days 7, 14, 21, 28, 42, 49, and 56.

Analysis Plan: The primary outcome measures were the change from baseline on the week 8 last-observation-carried-forward (LOCF) on-therapy evaluation. In addition to an LOCF analysis, an analysis of the observed data at each time point was performed using a parametric 2-way analysis of covariance (ANCOVA) with treatment and investigator as factors and the associated baseline as the covariate. The observed data and LOCF data analyses were applied to the primary and secondary variables. Changes from baseline for the primary and secondary efficacy variables (e.g., C-KIDDIE-SADS GAD [9 delineated items, severity component, impairment component, and complete], PARS, HAM-A, CGI-S, and SCARED scales), were analyzed at each time point.

Patient Disposition: Of the 158 subjects who entered the double blind period, 156 were analyzed for safety and 153 for efficacy (intent to treat), with 112 subjects ending up completing the study. The primary reasons that 45 (29%) subjects discontinued the study prematurely are identified in Table 8.1.1A, which was below provided by the sponsor in Final Study Report CSR-44734. "Failed to return" was the most frequent primary reason for discontinuation. Adverse events were the primary or a secondary cause for discontinuation of treatment for 2 (3%) of the venlafaxine ER-treated subjects and 7 (9%) subjects in the placebo group.

The disposition over time of all the subjects who entered the study is show in Table 8.1C taken from CSR-44734. The number who completed (C) and the number who discontinued (D) are shown by time period.

TABLE 8.1C. PATIENT STATUS OVER TIME: NUMBER OF PATIENTS - ON-THERAPY

	Placebo (n = 79)		Venlafaxine ER (n = 77)	
Time Period[a] (Days)	C[b,c]	D[b]	C	D
1 to 7	76	3	73	4
8 to 14	67	9	69	4
15 to 21	67	0	66	3
22 to 28	62	5	62	4
29 to 35	61	1	59	3
36 to 42	59	2	59	0
43 to 49	56	3	59	0
50 to 56	53	2	59	1

a: Does not include taper period.
b: C = the number of patients who completed the indicated time period; D = the number of patients who discontinued during each indicated time period.
c: If a patient completed early or missed a dose, they are not counted in the C column.
CDR 3-4ITDB (29 Mar 02)

The treatment groups were comparable in demographic and baseline characteristics (height, weight, duration of current episode, C- KIDDIE-SADS GAD (9 delineated items), C-KIDDIE-SADS (Complete), C-KIDDIE-SADS (Impairment), C-KIDDIE-SADS(Severity), PARS, HAM-A, SCARED parent, SCARED patient and the CGI-severity. Baseline characteristics of age, sex and ethnic origin are identified in Table 9.2.1A provided by the sponsor in CSR-44734.

TABLE 9.2.1A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS - INTENT-TO-TREAT POPULATION

Characteristic	Placebo (n = 77)	Venlafaxine ER (n = 76)	p-Value	Statistical Test[a]
Age (years)			.366	t
Mean	11.3	11.7		
SD	2.8	3.0		
Range	7.0 - 17.0	6.0 - 17.0		
Children, n (%)	42 (55)	39 (51)		
Adolescents, n (%)	35 (45)	37 (49)		
Sex, n (%)			.790	C
Female	31 (40)	29 (38)		
Male	46 (60)	47 (62)		
Ethnic origin, n (%)			.750	C
Arabic	1 (1)			
Asian	1 (1)	1 (1)		
Black	9 (12)	10 (13)		
Hispanic	3 (4)	5 (7)		
Other		1 (1)		
White	63 (82)	59 (78)		

The dose information for all subjects who were exposed to at least one single dose of venlafaxine ER (n= 77) is summarized in Table 10.1B. After the initial 7-day titration period, the mean daily doses of venlafaxine ER per body weight in kg were 1.4 mg/kg to 2.6-mg/kg-body weight.

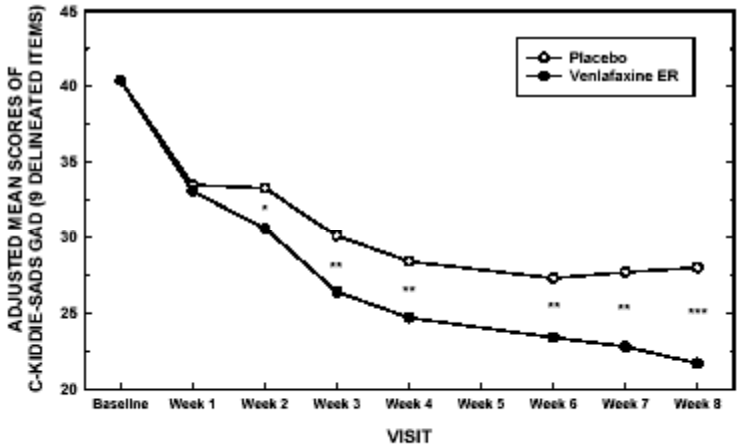
TABLE 10.1B. MEAN DAILY DOSE BY TIME INTERVAL

Time Interval (days)	n	Daily Dose Mean ± SD (mg/kg)
On-therapy[a]		
1-7	77	0.8 ± 0.3
8-14	73	1.4 ± 0.6
15-21	69	1.9 ± 0.6
22-28	66	2.1 ± 0.7
29-35	62	2.5 ± 0.9
36-42	59	2.6 ± 0.9
43-49	59	2.6 ± 0.9
50-56	59	2.6 ± 1.0
>56	31	2.6 ± 1.0
Taper	43	1.6 ± 0.5

a: On-therapy period excludes taper dose.
CDR 4-2ALL (21 Mar 02)

Results: On the primary outcome measure, venlafaxine ER was statistically more effective than placebo on the LOCF analyses for the mean scores on C-KIDDIE-SADS GAD (9 delineated items) total score at week 8 ($p < 0.001$), as well as weeks 2-7 ($p < 0.05$ at week 2, $p < 0.01$ at weeks 2-7). On the secondary outcome measures, venlafaxine ER was statistically more effective than placebo at week 8 on the LOCF mean scores for the C-KIDDIE-SADS GAD Severity total ($p < 0.001$), C-KIDDIE-SADS GAD Impairment total ($p = 0.002$), C-KIDDIE-SADS GAD Complete total ($p = 0.001$), PARS ($p < 0.001$), SCARED Parent total ($p = 0.007$), SCARED Patient total ($p = 0.002$), HAM- A total ($p = 0.003$) and CGI-S ($p < 0.001$). Table 9.41A, located in the Appendix, compares the LOCF analysis between treatment groups for the intent to treat subjects, and was provided by the sponsor in Final Study Report CSR-44734. These results are graphically displayed in Figure 9.4.1A in CSR-44734.

FIGURE 9.4.1A. ADJUSTED MEAN SCORES FOR THE C-KIDDIE-SADS GAD (9 DELINEATED ITEMS [LOCF ANALYSIS])



Conclusion(s): Based on the week 8 results (LOCF) of the C-KIDDIE-SADS GAD total score (9 delineated items), venlafaxine ER was shown to be significantly more effective than placebo for children and adolescents with GAD.

D. Efficacy Conclusions

Major Depressive Disorder In Children and Adolescents

For Studies 382 and 394, there were no differences between venlafaxine ER and placebo at week eight (8) on therapy, or, the last-observation-carried-forward (LOCF) on-therapy evaluation, as measured by the primary endpoint, CDRS-R total (382: P=0.338; 394: P=0.386). Hence, Venlafaxine ER is not effective in the treatment of Major Depressive Disorder in children and adolescents.

Generalized Anxiety Disorder In Children and Adolescents

For Studies 396 and 397, the primary efficacy was the last-observation-carried-forward (LOCF) week 8 on-therapy evaluations for the mean scores on the Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia GAD Subsection, 9 delineated items, total score (C-KIDDIE-SADS GAD). On this efficacy measure, non statistically significant improvement ($p = 0.06$) occurred in venlafaxine ER treated subjects compared to placebo at week 8 in study 396, while, in study 397, statistical superiority occurred in venlafaxine ER treated subjects compared to placebo at week 8 ($p < 0.001$). Hence, there is insufficient evidence at this time to conclude that venlafaxine ER is effective in the treatment of GAD.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety profile of venlafaxine ER in children and adolescents appears to be comparable to the safety profile in adults. Differences noted relate to: 1) the mean increase from baseline in the total serum cholesterol which was higher than adults in the pooled GAD, but, not in the pooled MDD trials; 2) a slightly higher mean pulse rate and ECG heart rate in children and adolescents than in adults; and 3) a smaller increase in height in children in the pooled GAD studies. Similarities in adverse events between children-adolescents and adults with venlafaxine ER use include 1) anorexia (2 times greater than placebo in both MDD and GAD); 2)weight loss; and 3) sustained increases in supine diastolic blood pressure. However, similar adverse event may impact the child-adolescent different than the same adverse

event in the adult. Hence, anorexia, decreased height attainment and elevated cholesterol may impact overall growth and development in the child-adolescent but not in the adult.

B. Description of Patient Exposure

Pooled safety data from the 2 double-blind studies reported in the depression supplement (382, 384) resulted in a safety population of 182 subjects who received at least 1 dose of venlafaxine ER and 179 subjects who received at least 1 dose of placebo for up to 8 weeks. The open label study (395) in MDD provides 86 subjects who received venlafaxine ER for up to 6 months. Hence, a total of 268 subjects who participated in these three studies received at least 1 dose of venlafaxine ER and 179 subjects received at least 1 dose of placebo.

Pooled safety data from the 2 double-blind studies reported in the GAD supplement (396, 397) resulted in a safety population of 157 subjects who received at least 1 dose of venlafaxine ER and 163 subjects who received at least 1 dose of placebo for up to 8 weeks.

Results from the phase 1 conduct disorder study (126) provide data on 25 subjects treated with venlafaxine IR for up to 6 weeks; 13 of those subjects were treated in an open-label extension for up to 2 years.

Major Depressive Disorder:

The sponsors table below shows the total sum of exposure for patients who took at least 1 dose of venlafaxine ER in the 3 depression studies in the safety database

TABLE 2.4.2A. PATIENT EXPOSURE YEARS FOR ALL TIME PERIODS—DEPRESSION STUDIES

	---------- Venlafaxine ER ----------		---------- Placebo ----------	
Study Number	Patients Who Received at Least 1 Dose	Patient Exposure Years	Patients Who Received at Least 1 Dose	Patient Exposure Years
B1-382	80	11.01	85	11.73
B1-394	102	15.95	94	15.47
Total double-blind	182	26.95	179	27.19
B1-395	86	30.24	N/A[a]	N/A
Total	268	57.19	179	27.19

a: N/A = not applicable.

The sponsors table below shows mean daily doses of venlafaxine ER by time interval, including the taper period.

TABLE 2.4.1B. MEAN DAILY DOSE OF VENLAFAXINE ER BY TIME INTERVAL—DEPRESSION STUDIES

Time Interval (days)	n	Daily Dose Mean ± SD (mg/kg)
On-therapy		
1 - 7	268	0.7 ± 0.3
8 - 14	262	1.3 ± 0.5
15 - 21	254	1.8 ± 0.6
22 - 28	237	2.0 ± 0.6
29 - 35	225	2.4 ± 0.8
36 - 42	216	2.4 ± 0.9
43 - 49	209	2.5 ± 0.8
50 - 60	198	2.6 ± 0.9
61 - 90	88	2.5 ± 0.8
91 - 120	58	2.6 ± 0.8
121 - 150	47	2.5 ± 0.8
151 - 180	44	2.5 ± 0.8
> 180	22	2.5 ± 0.8
Taper	128	1.5 ± 0.5

The demographic and baseline characteristics of all pooled subjects in the MDD trials are shown in the following table provided by the sponsor in the submission.

TABLE 2.5A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR ALL PATIENTS IN THE POOLED PHASE 3 STUDIES—DEPRESSION STUDIES

Characteristic	------ Placebo-controlled Studies----- Placebo (n = 179)	Venlafaxine ER (n = 182)	All 3 Studies Venlafaxine ER (n = 268)
Age, years[a]			
Mean	12.2	12.2	12.3
SD	2.7	2.6	2.7
Min-Max	7.0-17.0	7.0-17.0	7.0-17.0
Median	12.0	12.0	12.0
Group			
Children (7-12 years)	101	99	143
Adolescents (13-17 years)	78	83	125
Sex, n (%)			
Female	86 (48)	80 (44)	121 (45)
Male	93 (52)	102 (56)	147 (55)
Ethnic Origin, n (%)			
Arabic	0	2 (1)	2 (<1)
Asian	1 (<1)	3 (2)	4 (1)
Black	17 (9)	21 (12)	36 (13)
Hispanic	14 (8)	16 (9)	23 (9)
Native American	0	0	1 (<1)
White	146 (82)	134 (74)	194 (72)
Other	1 (<1)	6 (3)	8 (3)
Height, cm[b]			
Mean	154.0[c]	154.4	154.4
SD	15.4[c]	15.0	14.8
Min-Max	116.8-188.0[c]	120.7-190.5	120.7-190.5
Median	157.3[c]	154.9	155.2
Weight, kg[a]			
Mean	56.2	56.4	56.2
SD	20.3	20.8	20.6
Min-Max	22.3-123.8	25.0-129.5	25.0-129.5
Median	55.0	54.2	53.6

Abbreviation: Min-Max = minimum-maximum.
a: Determined at baseline.
b: Determined at prestudy visit.
c: Based on 178 patients.

Generalized Anxiety Disorder:
The sponsors table below shows the total sum of exposure for subjects who took at least 1 dose of venlafaxine ER in the 2 GAD studies in the safety database.

TABLE 3.4.2A. PATIENT EXPOSURE YEARS FOR ALL TIME PERIODS—GAD STUDIES

	---------- Venlafaxine ER ----------		---------- Placebo ----------	
Study Number	Patients Who Received at Least 1 Dose	Patient Exposure Years	Patients Who Received at Least 1 Dose	Patient Exposure Years
B2-396	80	13.08	84	13.56
B2-397	77	11.63	79	11.44
Total	157	24.71	163	25.01

The sponsors table below shows mean daily doses of venlafaxine ER by time interval, including the taper period.

TABLE 3.4.1B. MEAN DAILY DOSE BY TIME INTERVAL—GAD STUDIES

Time Interval (days)	n	Daily Dose Mean ± SD (mg/kg)
On-therapy		
1 - 7	157	0.8 ± 0.3
8 - 14	152	1.4 ± 0.5
15 - 21	145	1.9 ± 0.6
22 - 28	140	2.1± 0.6
29 - 35	134	2.5 ± 0.9
36 - 42	127	2.7 ± 0.8
43 - 49	126	2.7 ± 0.8
50 - 60	122	2.6 ± 0.9
> 60	24	2.5 ± 0.9
Taper	100	1.7 ± 0.5

The demographic and baseline characteristics subjects in the GAD trials are shown in the following tables provided by the sponsor in the submission: 1) all pooled subjects (Table 3.5A), 2) all children, 6-11 years (Table 3.5B) and 3) all adolescents, 12-17 years (Table 3.5C).

TABLE 3.5A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR ALL PATIENTS IN THE SAFETY POPULATION—GAD STUDIES

Characteristic	Placebo (n = 163)	Venlafaxine ER (n = 157)
Age, years[a]		
Mean	11.2	11.5
SD	2.6	3.1
Min-Max	6.0 - 17.0	6.0 - 17.0
Median	11.0	11.0
Group		
Children (6-11 years)	90	85
Adolescents (12-17 years)	73	72
Sex, n (%)		
Female	78 (48)	58 (37)
Male	85 (52)	99 (63)
Ethnic Origin, n (%)		
Arabic	2 (1)	0
Asian	1 (<1)	2 (1)
Black	16 (10)	17 (11)
Hispanic	17 (10)	18 (11)
Native American	0	1 (<1)
White	125 (77)	118 (75)
Other	2 (1)	1 (<1)
Height, cm[b]		
Mean	148.4[c]	149.8
SD	15.1[c]	16.4
Min-Max	111.8 - 184.2[c]	104.1 - 185.4
Median	147.3[c]	149.9
Weight, kg[a]		
Mean	50.3	50.3
SD	19.7	19.2
Min-Max	22.7 - 107.5	25.0 - 112.9
Median	45.0	47.1

Abbreviation: Min-Max = minimum-maximum.
a: Determined at baseline.
b: Determined at prestudy.
c: Based on 162 patients.

TABLE 3.5B. DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR CHILDREN (6–11 YEARS)—GAD STUDIES

Characteristic	Placebo (n = 90)	Venlafaxine ER (n = 85)
Age, (years)[a]		
Mean	9.3	9.0
SD	1.4	1.4
Min-Max	6.0 - 11.0	6.0 - 11.0
Median	9.0	9.0
Sex, n (%)		
Female	39 (43)	28 (33)
Male	51 (57)	57 (67)
Ethnic Origin, n (%)		
Arabic	1 (1)	0
Asian	1 (1)	1 (1)
Black	7 (8)	10 (12)
Hispanic	11 (12)	11 (13)
White	68 (76)	63 (74)
Other	2 (2)	0
Height, (cm)[b]		
Mean	138.8	138.9
SD	10.4	11.9
Min-Max	111.8 - 163.8	104.1 - 168.2
Median	137.2	139.7
Weight, (kg)[a]		
Mean	39.9	40.3
SD	13.0	14.2
Min-Max	22.7 – 83.2	25.0 - 90.4
Median	35.7	35.9

Abbreviation: Min-Max = minimum-maximum.
a: Determined at baseline.
b: Determined at prestudy.

TABLE 3.5C. DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR ADOLESCENTS (12-17 YEARS)—GAD STUDIES

Characteristic	Placebo (n = 73)	Venlafaxine ER (n = 72)
Age, (years)[a]		
Mean	13.6	14.5
SD	1.6	1.7
Min-Max	12.0 - 17.0	12.0 - 17.0
Median	13.0	14.5
Sex, n (%)		
Female	39 (53)	30 (42)
Male	34 (47)	42 (58)
Ethnic Origin, n (%)		
Arabic	1 (1)	0
Asian	0	1 (1)
Black	9 (12)	7 (10)
Hispanic	6 (8)	7 (10)
Native American	0	1 (1)
Other	0	1 (1)
White	57 (78)	55 (76)
Height, (cm)[b]		
Mean	160.5[c]	162.7
SD	10.7[c]	10.4
Min-Max	134.1 - 184.2[c]	137.2 - 185.4
Median	160.0[c]	162.6
Weight, (kg)[a]		
Mean	63.1	62.1
SD	19.0	17.7
Min-Max	36.1 - 107.5	33.1 - 112.9
Median	59.0	59.1

Abbreviation: Min-Max = minimum-maximum.
a: Determined at baseline.
b: Determined at prestudy.
c: Based on 72 patients.

C. Methods and Specific Findings of Safety Review

Major Depressive Disorder (MDD):

Serious Adverse Events: No subjects died during any of the 3 pediatric depression studies. In studies 382 and 394, the placebo-controlled studies, 14 of 182 (8%) venlafaxine ER treated subjects and 5 of 179 (3%) placebo treated subjects had serious adverse events. In the long- term, open-label study (395), 7 of 86 (8%) subjects treated with venlafaxine ER had serious adverse events. The sponsor has included Table 2.12.2A in the submission, which lists all subjects, by body system, who had serious adverse events. This table is included in the Appendix of this review.

In reviewing, the narratives of the subjects who developed serious adverse events, this reviewer's opinion was that some might have been probably related to venlafaxine ER. Behavior or depression worsening occurred in several subjects. The behavior or depression worsening consisted of the development of hypomania or mania (n=2-3), depression with psychotic features (n=2), worsening depression (n=2), suicide ideation or attempt (n=3-4) and aggressive behavior with homicidal ideation (n=1). An 11-year-old female with a positive family history of epilepsy had a brief (< 1 minute in duration), generalized tonic clonic seizure while on venlafaxine ER. A 13-year-old female, on 75 mg of venlafaxine ER, had a one-day history of moderately severe dizziness and nausea and possible syncope. A 15 year old male with a history of irritable bowel syndrome was treated with venlafaxine ER and had a 5.2 kg weight loss and also experienced transient tremors. An 11 y.o. BM with supraventricular tachycardia was found subsequently to have a baseline ECG consistent with Wolff-Parkinson-White syndrome. One subject developed aseptic meningitis, which was probably not related to study drug.

Adverse Events of Clinical Interest: Twenty-two (22) of 182 (12%) venlafaxine ER- treated subjects and 8 of 179 (4%) placebo treated subjects in the placebo-controlled studies (382 and 394) had adverse events of clinical interest. An adverse event of clinical interest was defined as "the Wyeth's medical monitor's assessment of the trial-emergent events, and, certain events (e.g., pregnancies, seizures, suicide attempts, symptomatic arrhythmias, overdoses, and abnormal liver function test results) that are always considered of potential clinical interest". This also included all adverse events that led to discontinuation that were not already included in the listing of patients with serious adverse events.

In the long-term, open- label study (395), 21 of 86 (24%) venlafaxine ER-treated subjects had adverse events of clinical interest. These are listed by the sponsor in Table 2.12.3A which is included in the Appendix.

Subject Withdrawals Due To Adverse Events: Of 268 venlafaxine ER-treated subjects in all 3 studies, 33 (12%) withdrew from the on-therapy period because of an adverse event. In the pooled placebo-controlled studies, 18 (10%) venlafaxine ER-treated subjects and 5 (3%) placebo-treated subjects withdrew from the on- therapy period because of an adverse event. The Treatment Emergent Adverse Events (TEAE's) leading to discontinuation from the on- therapy period for 1% of subjects in the venlafaxine ER treatment group in the pooled placebo-controlled studies was: hostility, manic reaction, overdose, and suicidal ideation. In addition, 1% of the venlafaxine ER treated subjects in all 3 studies discontinued because of a suicide attempt. Three (3) venlafaxine ER-treated subjects withdrew from the study because of vital sign or weight abnormalities. These consisted of a 1.8-kg weight loss by week 3 in a 7-year-old boy, tachycardia (standing pulse rate: + 20 at month 4) and syncope in a 13 year old female subsequently found to have hyperthyroidism, and increases in standing blood pressures from week 1 to week 3 (120/88: baseline to 140/110 at week 1 to 132/110 at week 3)in a 15 year old male. No subjects withdrew because of laboratory or ECG abnormalities. Table 2.11A from the sponsor's submission lists the TEAE's, by body system, leading to discontinuation for ≥ 1%% of the venlafaxine ER treated subjects in all 3 studies.

TABLE 2.11A. ADVERSE EVENTS CITED AS PRIMARY OR SECONDARY REASONS FOR DISCONTINUATION IN ≥ 1% OF THE VENLAFAXINE ER-TREATED PATIENTS WHO DISCONTINUED DURING THE ON-THERAPY PERIOD: NUMBER OF PATIENTS (%)— DEPRESSION STUDIES

	---------- Placebo-controlled --------		All 3 Studies
Body System Adverse Event	Placebo (n = 179)	Venlafaxine ER (n = 182)	Venlafaxine ER (n = 268)
Any adverse event	5 (3)	18 (10)	33 (12)
Body as a whole			
Overdose	1 (< 1)	2 (1)	2 (< 1)
Suicide attempt	0	1 (< 1)	3 (1)
Nervous system			
Hostility	1 (< 1)	3 (2)	6 (2)
Manic reaction	1 (< 1)	2 (1)	2 (< 1)
Suicidal ideation	0	4 (2)	5 (2)

Most Common TEAE's in 2 % Venlafaxine ER Subjects: The sponsor provides in the submission, Table 2.6.1.1 A of TEAEs with on-therapy incidences of at least 2% in venlafaxine ER

treated subjects in the pooled placebo-controlled studies by body system. Adverse events in italics are those that occurred more often with venlafaxine ER than with placebo. This table is included in the Appendix.

Most Common TEAE's in 5 % Venlafaxine ER Subjects:

The most common TEAEs with venlafaxine ER (incidence of ≥ 5% and at least 2 times greater than that observed with placebo) in the placebo-controlled depression studies were abdominal pain and anorexia. Abdominal pain was described as mild to moderate in severity, except for 1 subject in each group, lasting on the average for 1 day, and did not lead to discontinuation from the study. Anorexia was described as mild to moderate in severity, lasted from 4-104 days, usually was associated with abdominal pain, nausea, vomiting and weight loss not greater than 2 kg.

TABLE 2.6.1.2A. MOST COMMON TEAEs (≥ 5% WITH VENLAFAXINE ER *AND* AT LEAST 2 TIMES GREATER WITH VENLAFAXINE ER THAN WITH PLACEBO, EVALUATED BEFORE ROUNDING) DURING THE ON-THERAPY PERIOD: NUMBER (%) OF PATIENTS—POOLED PLACEBO-CONTROLLED DEPRESSION STUDIES

Body System Adverse Event	Placebo (n = 179)	Venlafaxine ER (n = 182)
Any adverse event	141 (79)	157[a] (86)
Body as a whole		
Abdominal pain	18 (10)	38 (21)
Digestive system		
Anorexia	4 (2)	13 (7)

Abbreviations: TEAEs = treatment-emergent adverse events.
a: Includes patient 394-0924, who had 1 on-therapy adverse event of clinical interest that was discovered after the database was locked, and was added by an erratum.

Laboratory Results in MDD:

Selected mean laboratory values for the MDD studies was provided by the sponsor in Table 2.7.2 A and is included in the Appendix. The adjusted mean changes from baseline with venlafaxine ER were not significantly different from those observed with placebo for any of the selected laboratory parameters, except for the final on therapy results for chloride. Total serum cholesterol with venlafaxine ER was not significantly increased from baseline at month 2 (0.012 mmol/L). The adjusted mean increase from baseline for total cholesterol with venlafaxine ER was not significantly different from the small but significant decrease with placebo. Total serum cholesterol with venlafaxine ER was not significantly increased from baseline after 6 months of treatment (0.087 mmol/ L). Two, venlafaxine ER treated subjects and 3 placebo-treated subjects had clinically important changes in laboratory values in studies 382 and 394; and, 2 venlafaxine ER-treated subjects had clinically important changes in laboratory

values in study 395. Two subjects in study 394, on venlafaxine ER, at mean daily doses of 70.9 mg and 167.8 mg, respectively developed transient elevations in AST/SGOT(26 to 89 mU/ml in one subject and 20 to 70 mU/ml in the other subject) and ALT/SGPT (27 to 113 mU/ml in one subject and 10 to 52 mU/ml in the other subject) which returned to normal after discontinuation of therapy. Two subjects in the placebo group in study 394 had increases in AST/SGOT and, or, ALT/SGPT. One of them had a past history of jaundice and had a transient elevation in AST/SGOT (29-53 mU/ml) and which returned to normal after therapy; and the other subject had a concurrent infection while in the study. The sponsor identifies these in the submission in Table 2.7.1.2A included in the Appendix.

Vital Sign Changes in MDD:

Blood Pressure:

In the depression studies, 4/268 (1%) of the venlafaxine ER-treated pediatric patients and no (0/179) placebo-treated patients were judged by the sponsor, by the criteria listed below to have had clinically important increases in blood pressure:

TABLE 2.8.1.1A. CRITERIA FOR DETERMINING POTENTIALLY CLINICALLY IMPORTANT CHANGES IN VITAL SIGNS AND WEIGHT

Variable	Criteria
Supine or standing pulse rate[a]	Increase of ≥ 15 beats/min to rate ≥ 120 beats/min or decrease of ≥ 15 beats/min to rate ≤ 50 beats/min
Supine or standing systolic blood pressure[a]	Increase of ≥ 20 mm Hg to ≥ 180 mm Hg or decrease of ≥ 20 mm Hg to ≤ 90 mm Hg
Supine or standing diastolic blood pressure[a]	Increase of ≥ 15 mm Hg to ≥ 105 mm Hg or decrease of ≥ 15 mm Hg to ≤ 50 mm Hg
Postural blood pressure change[b]	Decrease of ≥ 25 mm Hg systolic or ≥ 10 mm Hg diastolic when going from supine to standing position
Temperature[c]	≥ 101°F and a change of ≥ 2°F
Weight[d]	Change of ≥ 7% in body weight

a: Differences were measured from mean prestudy/baseline values.
b: Differences were measured from second supine to first standing value at each visit.
c: Differences were measured from prestudy value.
d: Differences were measured from baseline value.

A sustained elevation in supine diastolic blood pressure was defined as inclusive of all of the following: a treatment-emergent increase of 10-mm Hg or more from the mean of the prestudy/baseline values, on-therapy value above the age/sex/height-specific upper limit of normal from tables from Nelson Textbook of Pediatrics, and that these criteria be satisfied for at least 3 consecutive visits that were at least 7 days apart. Using these criteria, one subject (8-year-old male) in study 395 met the criteria for sustained increases in supine diastolic blood pressure. Hence, of the 268 venlafaxine ER treated patients in the 3 pediatric depression studies, 1

patient (0.4%) had a sustained increase in supine diastolic blood pressure. No placebo patient had a sustained increase in supine diastolic blood pressure.

The adjusted mean changes for the 2 groups were significantly different from each other between weeks 2 (week 2: supine systolic BP: -1.58: placebo, 2.27: venlafaxine ER) and 7 (week 7: supine systolic BP: -3.07: placebo, 1.93: venlafaxine ER). Similar but smaller mean changes were observed in supine and standing diastolic blood pressure (approximately 2-mm Hg increases with venlafaxine ER and 2 mm Hg decreases with placebo). The adjusted mean changes in diastolic blood pressure for the 2 treatment groups were significantly different from each other between weeks 3 (week 3: diastolic BP: -1.44: placebo, 1.43: venlafaxine ER) and 7 (week 7: diastolic BP: -2.60: placebo, 2.24: venlafaxine ER).

Pulse Rate:
In the placebo-controlled studies (382, 394), significant mean increases from baseline in standing and supine pulse rate with venlafaxine ER (2 to 5 beats/ min) were observed throughout the studies. The adjusted mean increases with venlafaxine ER were significantly different from the changes observed with placebo (1 to 2 beats/ min) at some time points.

Weight:
In the placebo-controlled studies, small (0.5 kg) mean decreases from baseline in weight in the venlafaxine ER group were significant. Those decreases from baseline with venlafaxine ER were significantly different ($p < 0.001$) from the gradual and significant increases (up to 1 kg) observed with placebo throughout the studies. The data from the 6- month, open- label study showed that after 6 months of treatment with venlafaxine ER, mean weight had increased slightly to a value higher than that at baseline (increase of 0.3 kg).

Height:
After 8 weeks of treatment, height was significantly increased from baseline (0.8 cm) for both treatment groups ($p < 0.001$) in the placebo-controlled studies. For subjects in study 395, height continued to increase to a mean increase from baseline of 1.2 cm at 6 months.

Comparison of Vital Sign Changes with Adults in MDD:
The results for vital signs and weight in the pediatric depression studies were comparable to the results in the adult

depression studies. The final on therapy increases in supine pulse rate in study 382 and 394 were 3 beats/min with venlafaxine ER and 1 beat/ min with placebo versus 2 beats/ min with venlafaxine ER and 1 beat/min with placebo in the adult controlled studies. In study 382 and 394, the final on- therapy mean increase and decrease, respectively, in supine diastolic blood pressures were 0.8 mm (venlafaxine ER) and 0.9 mm Hg (placebo) versus a mean increase and decrease, respectively, in adults of 1.2 mm Hg (venlafaxine ER) and a 0.2 mm Hg (placebo). In studies 382 and 394, and in the adults studies, a weight loss of ≥ 7% occurred in 3% of venlafaxine ER and 0.6%-1% of placebo subjects.

In studies 382 and 394, there was a significant mean increase from baseline in heart rate of 4 beats/min with venlafaxine ER. A significant decrease from baseline in QT interval (9 to 12 msec) with venlafaxine ER was significantly different from small increases with placebo. There were no significant changes from baseline with venlafaxine ER for QTc and there were no treatment group differences in QTc. The QTc interval was calculated by using Bazett's formula. In the 6-month, open-label study, there was no trend toward a further increase in heart rate and there were no significant changes from baseline in QTc at months 3 through 6. Clinically important ECG changes occurred in 3 venlafaxine ER and 5 placebo subjects in studies 382 and 394, and 2 venlafaxine ER subjects in the open label study (395).The sponsor lists the subjects with clinically important ECG results in Table 2.9.1.2A which is included in the Appendix of this review.

Generalized Anxiety Disorder (GAD):

Serious Adverse Events: No subjects died during any of the 2 pediatric GAD studies. In studies 396 and 397, the placebo-controlled studies, 2 of 157 (1%) venlafaxine ER treated subjects and 2 of 163 (1%) placebo treated subjects had serious adverse events. The sponsor has included Table 3.12.2A in the submission, which lists all subjects, by body system, who had serious adverse events. This table is included in the Appendix of this review.

Adverse Events of Clinical Interest: Fifteen(15) of 157 (10 %) venlafaxine ER treated subjects and 17 of 163 (10%) placebo treated subjects in the placebo-controlled studies (396 and 397) had adverse events of clinical interest. These are listed by the sponsor in Table 3.12.3A which is included in the Appendix.

Subject Withdrawals Due To Adverse Events: Of 157 venlafaxine ER-treated subjects in studies 396 and 397, 5 (3%) withdrew compared to 9 of 163(6%) placebo-treated subjects because of at least 1 adverse event. The Treatment Emergent Adverse Events (TEAE's) leading to discontinuation for the 1% venlafaxine ER treated subjects and 1% (n=2) placebo was abnormal/changed behavior (oppositional defiant behavior, acting out). No subjects withdrew because of abnormalities in laboratory, vital signs, weight, or ECG parameters.

Most Common TEAE's in 2 % Venlafaxine ER Subjects:
The sponsor provides in the submission, Table 3.6.1.1A of TEAEs with on-therapy incidences of at least 2% in venlafaxine ER treated subjects in the pooled placebo-controlled studies by body system. Adverse events in italics are those that occurred more often with venlafaxine ER than with placebo. This table is included in the Appendix.

Most Common TEAE's in 5 % Venlafaxine ER Subjects:
The most common TEAEs with venlafaxine ER (incidence of ≥ 5% and at least 2 times greater than that observed with placebo) in the placebo-controlled GAD studies were asthenia, pain, anorexia and somnolence. The asthenia was described as mild to moderate in severity, except for 3 venlafaxine ER subjects who had severe asthenia, lasting for greater than 1 day. Pain (mostly mouth and dental pain, leg pain, and general body aches) was described as mild in severity, except for 2 patients with moderately severe pain, lasting on average for 1 day, and according to the investigators were not related to treatment. Anorexia was described as mild to moderate in severity, lasted for ≥ 1 day(s), some was associated with abdominal pain, nausea, vomiting and weight loss of 1-2 kg. Somnolence was described as mild to moderate in severity, lasted for ≥ 1 day(s), with 1 subject having somnolence for 71 days. The investigator definitely related this to the study drug.

TABLE 3.6.1.2A. MOST COMMON TEAEs (≥ 5% *AND* AT LEAST 2 TIMES GREATER WITH VENLAFAXINE ER THAN WITH PLACEBO, EVALUATED BEFORE ROUNDING) DURING THE ON-THERAPY PERIOD: NUMBER (%) OF PATIENTS—GAD STUDIES

Body System Adverse Event	Placebo (n = 163)	Venlafaxine ER (n = 157)
Any adverse event	131 (80)	123 (78)
Body as a whole		
Asthenia	6 (4)	13 (8)
Pain	5 (3)	11 (7)
Digestive system		
Anorexia	5 (3)	20 (13)
Nervous system		
Somnolence	4 (2)	11 (7)

Abbreviation: TEAEs = treatment-emergent adverse events.

Laboratory Results in GAD:
There were significant mean increases from baseline in AST with venlafaxine ER and placebo and were not clinically significant (mean change in placebo: 2.0 and venlafaxine ER: 1.5 at final on therapy). There were also significant mean decreases from baseline in alkaline phosphatase with venlafaxine ER (mean change: -8.3 at final on therapy). However, the adjusted mean changes from baseline for the 2 treatment groups were not significantly different from each other for either parameter. Small but significant mean increases from baseline in total serum cholesterol were observed with venlafaxine ER (0.19 - 0.20 mmol/L). The adjusted mean increases from baseline were significantly different from the decreases from baseline with placebo (0.04 - 0.05 mmol/L). Final on-therapy mean increases from baseline for total serum cholesterol with venlafaxine ER in the 8-week placebo-controlled pediatric GAD studies (7.5 mg/dL) were larger than the final on therapy increases from baseline in the 8-week adult studies (1.0 mg/dL).

In the 2 GAD studies, 1 venlafaxine ER-treated patient (with a history of hypercholesterolemia) had a important increase in total cholesterol and 3 placebo-treated patients had important increases in AST and ALT. The subject on venlafaxine ER (dose 150 mg) was a 10 year old, over-weight, male with a history of hypercholesterolemia, hypertriglyceridemia on no concomitant medications who had an increase in total cholesterol (+ 0.74 mmol/L) and triglycerides (+ 2.33 mmol/L) at week 8.

Vital Sign Changes in GAD:

Blood Pressure:
In the GAD, 4 (3%) of the venlafaxine ER treated pediatric subjects and 2 (1%) placebo-treated subjects were judged by the sponsor to have had clinically important increases in blood pressure.

Standing and supine systolic blood pressure showed significant small mean increases from baseline with venlafaxine ER (2 - 3 mm Hg) and mean decreases from baseline with placebo (1 mm Hg). The adjusted mean changes were significantly different between the 2 treatment groups at most time points (supine systolic BP: placebo: mean changes [wk. 2: -1.25, final on therapy: -1.17]; venlafaxine ER: mean changes [wk 2: 2.05, final on therapy: 2.50]). A sustained elevation in supine diastolic blood pressure was defined as a treatment-emergent increase of 10-mm Hg or more from the mean of the prestudy/ baseline values. Using these

criteria, one subject (6-year-old female) on venlafaxine ER in study 397 met the criteria for sustained increases in supine diastolic blood pressure. The incidence of sustained increases in supine diastolic blood pressure with venlafaxine ER was 0.6% (1/157) in pediatric patients with GAD, compared with 0.5% (5/1011) in adults with GAD. No placebo patient had a sustained increase in supine diastolic blood pressure. Supine diastolic blood pressure increases were 2.2 mm Hg with venlafaxine ER compared with mean decreases of 0.5 mm Hg with placebo. In the adult studies, the mean increases with venlafaxine ER were 0.3 mm Hg compared with mean decreases of 0.9 mm Hg with placebo. No subjects in the pediatric GAD studies discontinued due to elevated blood pressure.

Pulse Rate:
In the placebo-controlled studies (396, 397), the final on therapy increase in supine pulse rates was 4 beats/min (venlafaxine ER) compared to 1 beat/min (placebo). In adult studies, the mean increase was 2 beats/ min with venlafaxine ER and 1 beat/ min with placebo. . The adjusted mean increases in supine pulse rate with venlafaxine ER were significantly different from increases with placebo at week 7 and final on-therapy visits ($p < 0.05$).

Weight:
Small (up to 0.6 kg) mean decreases from baseline in weight in the venlafaxine ER group occurred and were significant. These compares to the gradual increase in weight from baseline (up to 0.8 kg) in the placebo group, which also was significant. The adjusted mean changes from baseline with venlafaxine ER were significantly different from the changes with placebo.

Height:
Height was significantly increased from baseline after 8 weeks of treatment for both venlafaxine ER- treated and placebo-treated patients; however, the adjusted mean increase at month 2 in the placebo group (1.3 cm) was significantly higher than the increase in the venlafaxine ER group (0.4 cm).

ECG:
In studies 396 and 397, there was a significant mean increase from baseline in heart rate measured by ECG of 4 beats/min with venlafaxine ER. This increase was significantly different from a small but significant decrease in heart rate (approximately 2 beats/ min) with placebo. A significant decrease from baseline in QT interval (7 msec) with venlafaxine ER was significantly

different from a small, but significant increase from baseline with placebo (5 msec). A mean increase from baseline in QTc of 2.0 msec was observed at the final on- therapy visit with venlafaxine ER and a mean decrease of 1.0 msec was observed with placebo. The adjusted mean changes from baseline in QTc in the venlafaxine ER group were not significantly different from the changes in the placebo group. The QTc interval was calculated by using Bazett's formula.

D. Adequacy of Safety Testing

The safety testing as measured by vital signs, weight, height, ECG and laboratory testing was adequate. Subject exposure in the 6 month, open label safety trial was limited by a high drop out of 49/85 subjects (58 %).

E. Summary of Critical Safety Findings and Limitations of Data

There are no safety findings which should be included in the labeling. Venlafaxine may impact growth and development as a result of anorexia and resulting weight loss, and perhaps by causing a deceleration in growth. The latter is not certain in that opposite results were present for the MDD and the GAD studies.

VIII. Dosing, Regimen, and Administration Issues

No dosing recommendations can be made based upon these data, since efficacy in the pediatric populations for MDD and GAD were not established.

The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation I (OCPB/DPE-1) notes in their review of the two pharmacokinetic studies that exposure to venlafaxine is slightly lower in adolescents 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 pre-adolescents. 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".

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor performed subgroup analyses for the pooled data for MDD, and for GAD (396, 397) to determine the relationship

between a patient's sex and the incidence of the most common TEAEs. This was done by comparing the homogeneity of the odds ratios between the sexes. The sponsor used the Mantel-Haenszel method to calculate the odds ratio for the most common adverse events; the logit method if there was no report of a given adverse event for a particular group; and the Breslow-Day statistical test to compare the homogeneity of the odds ratios between patient subgroups.

In MDD, there were no significant differences between difference between girls and boys in the odds ratios for the most common TEAEs (abdominal pain or anorexia). In GAD, there were no significant differences between boys and girls in the odds ratios for asthenia, anorexia, or somnolence. There was a significant difference between boys and girls in the odds ratios for pain ($p = 0.03$). The sponsor states that the significant result was most likely due to the fact that no girls in the placebo group and 5 (9%) girls in the venlafaxine ER group reported the TEAE, whereas the incidence of pain for boys was similar in both treatment groups.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The sponsor performed a subgroup analysis on the pooled results from MDD in order to identify differential responses to venlafaxine ER in subgroups of the population. The sponsor used the following model to test the interaction between treatment on the primary efficacy parameter (LOCF) and subgroup factors (age, sex, race, etc.): Score = baseline + study site + treatment + subgroup factor + subgroup factor * treatment. If the interaction was not significant ($p > 0.10$), then the interaction term was dropped from the model and the effect of subgroup factor was tested as Score = baseline + study site + treatment + subgroup factor. For MDD, there was no interaction between therapy and age, or, therapy and sex., or, between therapy and ethnic origin. However, there was a significant effect for the effect of age/sex factor ($p = 0.041$), as indicated in sponsor's Table 2.4.3B which is included in the Appendix. For GAD the sponsor reports no interaction between therapy and age group, or, therapy and sex, or, between therapy and age and sex, or, between therapy and ethnic origin. The latter finding is different that that reported by the Division of Biometrics I (HFD-710) which reported a statistically significant reduction in C-KIDDIE-SADS GAD (9 delineated items) in the pooled data for studies 396 and 397 in white, but, not in non-white groups. The differences between these different analyses will need further exploration by Biometrics.

For MDD and GAD, individually, the sponsor examined the relationship between the patient's age and sex and the incidence of the most common TEAEs by comparing the homogeneity of the odds ratios among the age/sex groups. There were no significant differences among the odds ratios for age and sex subgroups for the adverse events for MDD or GAD.

For MDD and GAD, individually, the sponsor examined the relationship between the patient's race and the incidence of the most common TEAEs by comparing the homogeneity of the odds ratios between the ethnic groups. In MDD, there were no significant differences between ethnic groups in the odds ratios for either abdominal pain or anorexia, but, was limited by the small number of black/Hispanic subjects per treatment group. In GAD, there were no significant differences between ethnic groups in the odds ratios for any of the most common adverse events.

C. Evaluation of Pediatric Program

The pediatric program was adequate as defined by the sponsor conducting two, adequately powered, double blind, placebo controlled trials for each of the two indications (MDD and GAD). depressive disorder (85 [intent to treat], 36 [completers]). The open label study (395) in MDD provided 86 subjects who received venlafaxine ER for up to 6 months.

D. Comments on Data Available or Needed in Other Populations

No further sub-population studies are deemed to be indicated.

X. Conclusions and Recommendations

A. Conclusions

Based on the review of these supplement NDA's (20-151/SE5-024; 20-699/SE5-030), I conclude that venlafaxine is not effective in children and adolescents with major depressive disorder, or, with generalized anxiety disorder. Consistent with the sponsors representation, the safety profile in children and adolescents appears to be comparable to the safety profile in adults (e.g. anorexia, weight loss and sustained increases in supine diastolic blood pressure). Differences in safety present relate to: 1) a higher, total serum cholesterol in the pooled GAD, but, not in the pooled MDD trials; 2) a slightly higher mean pulse rate and ECG heart rate in children and adolescents than in adults; and 3) a smaller increase in height in children in the pooled GAD studies. Distinct (e.g. decreased height attainment) and similar adverse events in the child-adolescent (e.g.

anorexia, elevated cholesterol) may impact overall growth and development in the child-adolescent but not in the adult.

B. Recommendations

I recommend that the Division take a non-approvable action for supplement NDA's (20-151/SE5-024; 20-699/SE5-030).

XI. Appendix

A. Draft Labeling Review

Since I am not recommending approval for these two indications, no labeling review was completed by the undersigned.

_____, February 13, 2003
Glenn B. Mannheim, M.D., Date

cc: NDA: 20-151, SE5-024
NDA: 20-699, SE5-030
HFD 120/
P David
G Mannheim
G Dubitsky
P Andreason
T Laughren
R Katz
R Kavanagh
F Kong

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B. Tables

1. Table 2.1A Venlafaxine ER: Phase 3 MDD Studies

TABLE 2.1A. VENLAFAXINE ER PHASE 3 DEPRESSION STUDIES

Protocol No. Report No. (Country) Investigator(s) *Location in Submission*	Study Start-End Dates	Study Design	Diagnosis / Criteria for Inclusion	Test Product / Reference Therapy	Route,[a] Dose, Frequency (Duration of Treatment)	No. Enrolled in Study	Sex, n/n Age Range, (Mean Age), Race, n (%)
0600B1-382-US CSR-43456 (United States) (b) (4) *Location in Submission to be added* CRT CRF	10/97-9/00	Multicenter, parallel group, 14 ± 3-day single-blind placebo, followed by 8-week DB (venlafaxine ER or placebo); stratified by age group; taper at end of study.	Outpatient children (7-12 years old) or adolescents (13-17 years old), who met DSM-IV and KIDDIE-SADS-PL criteria for major depressive disorder at prestudy and had • minimum prestudy and study baseline scores of > 40 on the CDRS-R and no greater than 30% decrease in CDRS-R score between prestudy and study baseline, • CGI severity of illness score ≥ 4 at baseline, • depressive symptoms for at least 1 month before entry into the study.	Ven ER / Placebo	Dose by body weight (mg/day): Days 1-7 all weights: 37.5 Days 8-14 25-39 kg: 37.5 or 75 ≥ 40 kg: 75 Days 15-28 25-39 kg: 37.5 or 75 40-49 kg: 75 or 112.5 ≥ 50 kg: 75 or 150 Days 29-56 25-39 kg: 37.5, 75, or 112.5 40-49 kg: 75, 112.5, or 150 ≥ 50 kg: 75, 150, or 225 (8 weeks DB)	Planned: 158 Enrolled: 166 Safety: 165 Efficacy: 161	F 83 M 82 7 to 17 yrs (Ven ER, 12.3 yrs; Pbo, 12.2 yrs) W 145 (88) B 13 (8) H 6 (4) O 1 (1)

Protocol No. Report No. (Country) Investigator(s) *Location in Submission*	Study Start-End Dates	Study Design	Diagnosis / Criteria for Inclusion	Test Product / Reference Therapy	Route,[a] Dose, Frequency (Duration of Treatment)	No. Enrolled in Study	Sex, n/n Age Range, (Mean Age), Race, n (%)
0600B1-394-US CSR-44693 (United States) (b) (4)	8/00-8/01	Multicenter, parallel group, 4- to 10-day single-blind placebo, followed by 8-week DB (venlafaxine ER or placebo); stratified by age group; taper at end of study.	Outpatient children (7-12 years old) or adolescents (13-17 years old), who met DSM-IV and KIDDIE-SADS-PL criteria for major depressive disorder at prestudy and had • minimum prestudy and study baseline scores of > 40 on the CDRS-R and no greater than 30% decrease in CDRS-R scores between prestudy and study baseline, • CGI severity of illness score ≥ 4 at both prestudy and baseline, • depressive symptoms for at least 1 month before entry into the study.	Ven ER / Placebo	Dose by body weight (mg/day): Days 1-7 all weights: 37.5 Days 8-14 25-39 kg: 37.5 or 75 ≥ 40 kg: 75 Days 15-28 25-39 kg: 37.5 or 75 40-49 kg: 75 or 112.5 ≥ 50 kg: 75 or 150 Days 29-56 25-39 kg: 37.5, 75, or 112.5 40-49 kg: 75, 112.5, or 150 ≥ 50 kg: 75, 150, or 225 (8 weeks DB)	Planned: 124 Enrolled: 201 Safety: 196 Efficacy: 193	F 83 M 113 7 to 17 yrs (All, 12.2 yrs; ven ER, 12.2 yrs; Pbo, 12.1 yrs) W 135 (69) B 25 (13) H 24 (12) A 4 (2) Ar 2 (1) O 6 (3)

2. Table 3.1A Venlafaxine ER: Phase 3 GAD Studies

Protocol No. Report No. (Country) Investigator(s) *Location in Submission*	Study Start-End Dates	Study Design	Diagnosis / Criteria for Inclusion	Test Product / Reference Therapy	Route,[a] Dose, Frequency (Duration of Treatment)	No. Enrolled in Study	Sex, Age Range, (Mean Age), Race, n (%)
0600B2-396-US CSR-44723 (United States) (b) (4)	8/00-9/01	Multicenter, parallel group, 4- to 10-day single-blind placebo, followed by 8-week DB (venlafaxine ER or placebo); stratified by age group. Taper at end of study.	Outpatient children (6-11 years old) or adolescents (12-17 years old), who met DSM-IV and C-KIDDIE-SADS GAD criteria; had minimum prestudy and study baseline scores on the C-KIDDIE-SADS GAD as follows: • ≥ 20 on severity component, • ≥ 7 on impairment component, • ≥ 4 on following 3 items of severity component: severity of anxiety and worry, difficulty controlling worrying, severity of associated symptoms,	Ven ER / Placebo	Dose by body weight (mg/day): Days 1-7 all weights: 37.5 Days 8-14 25-39 kg: 37.5 or 75 ≥ 40 kg: 75 Days 15-28 25-39 kg: 37.5 or 75 40-49 kg: 75 or 112.5 ≥ 50 kg: 75 or 150 Days 29-56 25-39 kg: 37.5, 75, or 112.5 40-49 kg: 75, 112.5, or 150 ≥ 50 kg: 75, 150, or 225 (8 weeks DB)	Planned: 140 Enrolled: 164 Safety: 164 Efficacy: 160	F 74 M 90 6 to 17 yrs (All, 11.2 yrs; Ven ER, 11.4 yrs; Pbo, 11.1 yrs) W 118 (72) B 14 (9) H 27 (16) Nat Am 1 (1) A 1 (1) Ar 1 (1) O 2 (1)

Protocol No. Report No. (Country) Investigator(s) *Location in Submission*	Study Start-End Dates	Study Design	Diagnosis / Criteria for Inclusion	Test Product / Reference Therapy	Route,[a] Dose, Frequency (Duration of Treatment)	No. Enrolled in Study	Sex, Age Range, (Mean Age), Race, n (%)
(0600B2-396-US (b) (4) *Location in Submission to be added* CRT CRF			• ≥ 4 on following 2 items of severity component: frequency of anxiety and worry during average week, frequency of associated symptoms during average week, • ≥ 4 on following item of impairment component: global impairment functioning. Also, had CGI severity of illness score ≥ 4 at prestudy and baseline, CDRS-R < 45 at prestudy and baseline, and anxiety symptoms for at least 6 months before entry into the study.				

Protocol No. Report No. (Country) Investigator(s) *Location in Submission*	Study Start-End Dates	Study Design	Diagnosis / Criteria for Inclusion	Test Product / Reference Therapy	Route,[a] Dose, Frequency (Duration of Treatment)	No. Enrolled in Study	Sex, Age Range, (Mean Age), Race, n (%)
0600B2-397-US CSR-44734 (United States) (b) (4)	4/00-8/01	Multicenter, parallel group, 4- to 10-day single-blind placebo, followed by 8-week DB (venlafaxine ER or placebo); stratified by age group. Taper at end of study.	Outpatient children (6-11 years old) or adolescents (12-17 years old), who met DSM-IV and C-KIDDIE-SADS GAD criteria; had minimum prestudy and study baseline scores on the C-KIDDIE-SADS GAD as follows: • ≥ 20 on severity component, • ≥ 7 on impairment component, • ≥ 4 on following 3 items of severity component: severity of anxiety and worry, difficulty controlling worrying, severity of associated symptoms,	Ven ER / Placebo	Dose by body weight (mg/day): Days 1-7 all weights: 37.5 Days 8-14 25-39 kg: 37.5 or 75 ≥ 40 kg: 75 Days 15-28 25-39 kg: 37.5 or 75 40-49 kg: 75 or 112.5 ≥ 50 kg: 75 or 150 Days 29-56 25-39 kg: 37.5, 75, or 112.5 40-49 kg: 75, 112.5, or 150 ≥ 50 kg: 75, 150, or 225 (8 weeks DB)	Planned: 140 Enrolled: 158 Safety: 156 Efficacy: 153	F 62 M 94 6 to 17 yrs (All, 11.5; ven ER, 11.7 yrs; Pbo, 11.3 yrs) W 125 (80) B 19 (12) H 8 (5) A 2 (1) Ar 1 (< 1) O 1 (< 1)

Protocol No. Report No. (Country) Investigator(s) *Location in Submission*	Study Start-End Dates	Study Design	Diagnosis / Criteria for Inclusion	Test Product / Reference Therapy	Route,[a] Dose, Frequency (Duration of Treatment)	No. Enrolled in Study	Sex, Age Range, (Mean Age), Race, n (%)
(0600B2-397-US continued) *Location in Submission to be added* CRT CRF			• ≥ 4 on following 2 items of severity component: frequency of anxiety and worry during average week, frequency of associated symptoms during average week, • ≥ 4 on following item of impairment component: global impairment functioning. Also, had CGI severity of illness score ≥ 4 at prestudy and baseline, CDRS-R < 45 at prestudy and baseline, and anxiety symptoms for at least 6 months before entry into the study.				

3. Listing of Investigators/Sites for Study: 0600B1-382-US (382):

(b) (4)

4. Listing of Investigators/Sites for Study: 0600B1-394-US (394):

(b) (4)

[20] DSI determined that study irregularities occurred at this site, hence, all data from this site will be excluded.

(b) (4)

5. Listing of Investigators/Sites for Study: 0600B2-396-US (396):

(b) (4)

6. Listing of Investigators/Sites for Study: 0600B2-397-US (397):

7. Table 9.41A: Comparison Between Treatment Groups-Study 396:

TABLE 9.4.1A. COMPARISON BETWEEN TREATMENT GROUPS FOR C-KIDDIE-SADS GAD 9 DELINEATED ITEMS (INTENT-TO-TREAT PATIENTS) - LOCF ANALYSIS

Week on-therapy	Therapy Group	Number of Patients	Mean Score	Change From Baseline	Adj Change From Baseline	Standard Error	Adj Means (95% CI)	Placebo Minus Ven ER Adj Means (95% CI)	p-Values F-test
Baseline	Placebo	82	39.7				39.5 (39.5,39.5)		
	Venlafaxine ER	78	39.3				39.5 (39.5,39.5)		
Week 1	Placebo	81	35.2	-4.4	-4	0.8	35.5 (34.0,37.0)		0.276
	Venlafaxine ER	74	34.6	-4.7	-5	0.8	34.5 (33.0,36.0)	1.0 (-0.8,2.9)	
Week 2	Placebo	82	31.2	-8.4	-7.9	1.01	31.6 (29.6,33.6)		0.486
	Venlafaxine ER	77	30.4	-8.9	-8.8	1	30.7 (28.8,32.7)	0.9 (-1.6,3.3)	
Week 3	Placebo	82	29.9	-9.8	-9.1	1.06	30.3 (28.1,32.5)		0.257
	Venlafaxine ER	78	28.1	-11.2	-10.7	1.04	28.8 (26.7,30.9)	1.5 (-1.1,4.2)	
Week 4	Placebo	82	29.6	-10.1	-9.6	1.03	29.9 (27.7,32.1)		0.088
	Venlafaxine ER	78	27.2	-12.1	-11.9	1.04	27.6 (25.5,29.7)	2.3 (-0.3,5.0)	
Week 6	Placebo	82	28.6	-11.1	-11.8	1.11	27.7 (25.3,30.1)		0.180
	Venlafaxine ER	78	25.6	-13.6	-13.8	1.18	25.7 (23.4,28.0)	2.0 (-0.9,4.9)	
Week 7	Placebo	82	26	-13.7	-13.9	1.2	25.6 (23.1,28.1)		0.342
	Venlafaxine ER	78	23.7	-15.6	-15.3	1.16	24.2 (21.8,26.6)	1.5 (-1.5,4.5)	
Week 8	Placebo	82	26.7	-13	-12.6	1.17	26.9 (24.4,29.4)		0.060
	Venlafaxine ER	78	23.5	-15.8	-15.5	1.12	24.0 (21.6,26.4)	2.9 (-0.1,5.9)	
Final	Placebo	82	26.8	-12.9	-12.7	1.17	26.8 (24.3,29.3)		0.075
	Venlafaxine ER	78	23.6	-15.7	-15.5	1.12	24.0 (21.6,26.4)	2.8 (-0.2,5.8)	

8. Table 9.41A: Comparison Between Treatment Groups-Study 397:

TABLE 9.4.1A. COMPARISON BETWEEN TREATMENT GROUPS FOR C-KIDDIE-SADS GAD TOTAL (9 DELINEATED ITEMS) LOCF ANALYSIS

Time on Therapy	Therapy Group	Number of Patients	Mean Score	Adj. Change From Baseline	Standard Error	Adj Means (95% CI)		Placebo Minus Ven ER Adj. Means	p-Value F-test
Baseline	Placebo	77	40.3			40.4	(40.4 - 40.4)		
	Ven-ER	76	40.4			40.4	(40.4 - 40.4)		
Week 1	Placebo	74	36.1	-6.8	0.86	33.5	(31.8 - 35.1)		.683
	Ven-ER	76	35.7	-7.2	0.87	33.1	(31.6 - 34.6)	0.4 (-1.4 - 2.1)	
Week 2	Placebo	77	34.9	-7.1	0.91	33.3	(31.3 - 35.3)		.021
	Ven-ER	76	32.7	-9.8	1.02	30.6	(28.6 - 32.5)	2.7 (0.4 - 5.0)	
Week 3	Placebo	77	32.8	-10.3	1.02	30.1	(27.8 - 32.3)		.005
	Ven-ER	76	29.9	-13.9	1.08	26.4	(24.2 - 28.6)	3.7 (1.1 - 6.2)	
Week 4	Placebo	77	31.7	-12.0	0.93	28.4	(25.9 - 30.8)		.009
	Ven-ER	76	28.2	-15.7	1.19	24.7	(22.3 - 27.0)	3.7 (1.0 - 6.4)	
Week 6	Placebo	77	30.3	-13.0	1.12	27.3	(24.8 - 29.8)		.007
	Ven-ER	76	27.1	-17.0	1.15	23.4	(20.9 - 25.8)	4.0 (1.1 - 6.8)	
Week 7	Placebo	77	30.0	-12.7	1.08	27.7	(25.0 - 30.4)		.002
	Ven-ER	76	25.7	-17.5	1.12	22.8	(20.2 - 25.4)	4.8 (1.8 - 7.9)	
Week 8	Placebo	77	30.2	-12.4	1.18	28.0	(25.1 - 30.8)		<.001
	Ven-ER	76	24.8	-18.6	1.16	21.7	(19.0 - 24.5)	6.2 (3.0 - 9.5)	
Final	Placebo	77	30.2	-12.5	1.19	27.9	(25.1 - 30.7)		<.001
	Ven-ER	76	24.8	-18.7	1.16	21.7	(18.9 - 24.4)	6.2 (3.0 - 9.4)	

Abbreviations: C-KIDDIE-SADS GAD = Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia; LOCF = last observation carried forward; Ven ER = venlafaxine extended release.
EFF397.lst 26 Mar 2002

9. Serious Adverse Events in MDD

TABLE 2.12.2A. LISTING OF PATIENTS WITH SERIOUS ADVERSE EVENTS—DEPRESSION STUDIES

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term[c]	Discontinuation Because of Adverse Event[d]
Venlafaxine ER							
Body as a whole							
38205-019[e]	8/F	37.5	1.2	0[f]	13	Overdose	Yes
38211-012	10/F	81.8	1.7	75.0	43	Suicide attempt	Yes
394-1684	14/M	125.7	2.43	150.0	21	Accidental injury (fall)	No
395-0302	12/M	112.5	1.65	0	34[g]	Suicide attempt	Yes
395-0305	17/F	55.0	1.14	75.0	11	Suicide attempt	Yes
Nervous system							
38202-006	9/M	78.8	2.8	0	94 (poststudy)	Depression	No
38202-016	16/M	80.0	0.8	150.0	34	Manic reaction	Yes
				75.0	35	Sleep disorder (sleep disturbance)	Yes
38204-023	11/F	86.3	1.9	150.0	30	Convulsion	Yes
38205-008[e,h]	12/M	65.6	1.7	0	29[g]	Suicidal ideation	Yes
				0	29	Hallucinations	No
38207-017	12/M	67.6	1.3	0	62 (poststudy)	Emotional lability (worsening mood)	No
38209-009	15/M	103.3	0.8	150.0	43	Meningitis	Yes
38209-020	13/F	37.5	0.6	37.5	13	Suicidal ideation	Yes
38209-023	13/M	37.5	0.9	37.5	4	Hostility (verbally aggressive)	Yes
394-0041	7/M	56.3	2.21	0	29[g]	Suicidal ideation	Yes
394-0126	14/M	51.8	0.97	75.0	21	Suicidal ideation, hostility (homicidal ideation)	Yes
394-1087[e]	16/M	118.5	1.77	150.0	47	Agitation	Yes
				150.0	50	Hostility (aggressive behavior)	Yes

TABLE 2.12.2A. LISTING OF PATIENTS WITH SERIOUS ADVERSE EVENTS—DEPRESSION STUDIES

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term[c]	Discontinuation Because of Adverse Event[d]
395-0341	12/M	50.9	0.72	75.0	9	Hallucinations	Yes
395-0421	12/M	146.5	1.94	0	76[g]	Depression	Yes
				0	76	Hostility (homicidal ideation)	Yes
				0	76	Suicidal ideation	Yes
395-0544	11/F	64.3	0.89	75.0	28	Hostility (bouts of violence)	Yes
Respiratory system							
395-0186	13/M	32.8	0.35	0	9[g]	Pharyngitis	Yes
Placebo							
Body as a whole							
38207-008[i]	12/M	N/A		N/A	80 (poststudy)	Intentional injury (scratching on his arms)[j]	No
38207-023	14/F	N/A		N/A	3	Overdose	Yes
Nervous system							
38202-036	13/F	N/A		N/A	87 (poststudy)	Hostility	No
38207-008[i]	12/M	N/A		N/A	80 (poststudy)	Suicidal ideation	No
38209-013	12/M	N/A		N/A	15	Hostility (sexually aggressive behavior), nervousness (irritability)[j]	Yes
38209-027[e]	17/M	N/A		N/A	23[g]	Manic reaction	Yes

TABLE 2.12.2A. LISTING OF PATIENTS WITH SERIOUS ADVERSE EVENTS—DEPRESSION STUDIES

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term[c]	Discontinuation Because of Adverse Event[d]

Abbreviation: N/A = not applicable.
a: Age at baseline.
b: Calculated by using baseline weight.
c: Verbatim terms are included in parentheses for vague COSTART terms.
d: Discontinuation due to listed serious adverse event.
e: Blind was broken at the time of the adverse event.
f: Overdose occurred 6 days after the last known dose, which was on day 7.
g: Onset of adverse event was 1 or more days after the last *full* dose of study drug. 395-0302: 2 days; 38205-008: 1 day; 394-0041: 1 day; 395-0421: 12 days (1 day posttaper); 395-0186: 1 day; 38209-027: 2 days.
h: 15-day IND safety report was filed.
i: Patient listed in table more than once because he or she had serious adverse events in more than 1 body system category.
j: Serious adverse event was discovered after the database was locked and was added by erratum.

10. Adverse Events of Clinical Interest in MDD

TABLE 2.12.3A. LISTING OF PATIENTS WITH OTHER ADVERSE EVENTS OF CLINICAL INTEREST— DEPRESSION STUDIES

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term[c]	Discontinuation Because of Adverse Event
Venlafaxine ER							
Body as a whole							
394-0405	14/F	119.6	2.01	150.0	51	Intentional injury (cut arm deliberately)	No
394-0571[d]	10/F	37.5	0.80	37.5	1	Chest pain	Yes
394-1080[d]	12/M	62.5	0.94	75.0	17	Headache	Yes
394-1366	17/F	165.8	1.97	37.5	5	Intentional injury (self-mutilation)	No
394-1561	12/F	83.0	1.07	0[e,h]	44	Overdose	Yes
395-0100	16/M	119.7	2.44	150.0	32	Intentional injury (self-mutilation, cuts on arms)	No
395-0153	8/M	97.5	3.27	0	185 (poststudy)	Discontinuation symptoms	No
Cardiovascular system							
38209-004	13/F	67.3	1.1	75.0	10	Syncope	No
38211-021	11/M	77.6	2.8	112.5	42	Supraventricular tachycardia[f]	No
394-0056	15/M	61.5	0.74	75.0	22	Hypertension	Yes
394-0371	17/F	100.6	1.54	75.0	34	Syncope	No
394-1087	16/M	118.5	1.77	150.0	50	Hypertension, tachycardia	No
395-0267[d]	16/F	176.4	3.15	150.0	28	Tachycardia	No
395-0269[d,g]	16/F	156.5	1.63	75.0, 225.0, 150.0	42, 126, 189	Hypertension	No
395-0340	13/F	65.3	1.36	75.0	21	Syncope	No
				75.0	119	Tachycardia	Yes
395-0350	13/F	120.8	1.78	187.5	154	ECG abnormal (rightward axis)	No

TABLE 2.12.3A. LISTING OF PATIENTS WITH OTHER ADVERSE EVENTS OF CLINICAL INTEREST— DEPRESSION STUDIES

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term[c]	Discontinuat Because o Adverse Eve
Digestive system							
394-0681[d]	15/F	50.0	1.22	0[h]	20	Nausea	Yes
395-0104	17/F	178.8	2.79	225.0	93	Nausea	Yes
395-0114	10/M	18.8	0.48	37.5	1	Gastroenteritis	Yes
395-0115	11/M	169.4	2.46	225.0	71	Dyspepsia	Yes
				225.0	71	Vomiting	Yes
Hemic and lymphatic							
395-0160	8/F	92.3	3.06	112.5	63	Eosinophilia	No
Metabolic and nutritional							
394-0449	14/M	85.0	1.47	75.0	14	Weight loss	No
394-0921	15/M	70.9	0.79	75.0	56	AST/SGOT and ALT/SGPT increased	No
394-1563	11/M	67.2	1.87	75.0	51	Weight gain	No
395-0261[d]	7/M	62.5	2.48	75.0	21	Weight loss	Yes
395-0263	11/F	176.4	2.60	0[h]	126	Weight gain	No
				225.0	189	Weight gain	No
395-0265	10/M	62.9	1.62	112.5	149	Weight loss	No
395-0267[d]	16/F	176.4	3.15	225.0	91	Weight loss	No
395-0269[d]	16/F	156.5	1.63	150.0	56	Weight loss	No
395-0306	14/F	81.8	1.92	75.0	14	Weight loss	No
Nervous system							
38202-100	10/M	46.9	1.4	75.0	23	Manic reaction	Yes
38204-023	11/F	86.3	1.9	112.5	21	Suicidal ideation	No
38209-028	10/M	37.5	1.0	37.5	15	Hallucinations, paranoid reaction	Yes
394-0523	17/M	155.4	2.79	225.0	62	Hostility (angry)	No

TABLE 2.12.3A. LISTING OF PATIENTS WITH OTHER ADVERSE EVENTS OF CLINICAL INTEREST— DEPRESSION STUDIES

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term[c]	Discontinuation Because of Adverse Event
394-0563	14/F	117.2	1.48	150.0	48	Anxiety	No
				75.0	56	Anxiety	No
394-0564	9/F	65.6	1.20	0	56 (poststudy)	Hostility (increased anger)	No
394-0681[d]	15/F	50.0	1.22	112.5	16	Confusion, somnolence	No
394-0924[d]	17/M	121.4	1.66	150.0	41	Hostility (aggressive outburst)	No
394-1080[d,i]	12/M	62.5	0.94	75.0	12	Nervousness (irritability)	Yes
				75.0	12	Agitation, hostility (rage)	No
394-1322	7/F	82.4	2.59	75.0	10, 30	Hostility (aggressive behavior)	No
395-0150	7/M	43.1	1.62	37.5	17	Torticollis	Yes
395-0181	12/F	106.7	1.43	112.5	158	Hostility (aggression)	No
395-0261[d]	7/M	62.5	2.48	75.0	8	Abnormal/changed behavior (increased impulsivity, increased oppositionality)	Yes
				75.0	14	Nervousness (increased irritability)	Yes
395-0264	8/M	30.0	0.80	0[h]	3	Insomnia	Yes
				37.5	5	Hyperkinesia (hyperactivity increased), emotional lability (mood swings)	Yes
395-0347	10/M	74.2	1.39	75.0	167	Abnormal/changed behavior (uninhibited behavior)	No
395-0382	17/F	109.6	2.36	150.0	54	Obsessive-compulsive symptoms (self-abusive)	No
395-0582	7/M	39.5	1.28	75.0	31	Abnormal/changed behavior (impulsivity)	No
Respiratory system							
394-0571[d]	10/F	37.5	0.80	37.5	1	Stridor, dyspnea	Yes

TABLE 2.12.3A. LISTING OF PATIENTS WITH OTHER ADVERSE EVENTS OF CLINICAL INTEREST— DEPRESSION STUDIES

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term[c]	Discontinuation Because of Adverse Event
Skin and appendages							
395-0220	14/F	87.0	2.12	75	14	Pruritus	Yes
Placebo							
Body as a whole							
38204-024[d]	13/F	N/A		N/A	20	Headache	Yes
Cardiovascular system							
38204-100	12/F	N/A		N/A	42	Hypotension	No
394-0604[d]	12/F	N/A		N/A	30	Hypotension	No
394-0846	16/F	N/A		N/A	58	Sinus bradycardia	No
Digestive system							
394-0321	7/M	N/A		N/A	55	Liver function tests abnormal	No
Hemic and lymphatic system							
38209-006	15/M	N/A		N/A	63	Leukopenia	No
Metabolic and nutritional							
394-1086	11/M	N/A		N/A	54	AST/SGOT and ALT/SGPT increased	No
Nervous system							
38204-024[d]	13/F	N/A		N/A	9	Dizziness	Yes
394-0604[d]	12/F	N/A		N/A	5	Abnormal/changed behavior (hair pulling)	No
				N/A	24	Hostility (aggressiveness)	No
394-1685	15/M	N/A		N/A	30	Insomnia, nervousness (increased irritability)	Yes
Respiratory system							
38204-024[d]	13/F	N/A		N/A	22	Rhinitis	Yes

TABLE 2.12.3A. LISTING OF PATIENTS WITH OTHER ADVERSE EVENTS OF CLINICAL INTEREST— DEPRESSION STUDIES

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term[c]	Discontinuation Because of Adverse Event

Abbreviations: ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; N/A = not applicable.

a: Age at baseline.
b: Calculated by using baseline weight.
c: Verbatim terms are included in parentheses for vague COSTART terms.
d: Patient listed in table more than once because he or she had adverse events of clinical interest in more than 1 body system category.
e: Total daily dose does not include the amount of the overdose.
f: Cardiologist consultation 1 month after poststudy visit confirmed that the condition was present prestudy.
g: Clinically important hypertension was also present prestudy.
h: Noncompliant on the day of the adverse event.
i: Reports of adverse events of clinical interest were discovered after the database was locked and were added by errata.

11. Most Common TEAE's in 2 % Venlafaxine ER Subjects in MDD

TABLE 2.6.1.1A. COMMON TEAEs (≥2% IN THE VENLAFAXINE ER GROUP IN THE POOLED PLACEBO-CONTROLLED STUDIES): NUMBER (%) OF PATIENTS DURING THE ON-THERAPY PERIOD—DEPRESSION STUDIES

	---------- Placebo-controlled Studies ----------	
Body System Adverse Event	Placebo (n = 179)	Venlafaxine ER (n = 182)
Any adverse event	141 (79)	157[a] (86)
Body as a whole		
Abdominal pain[b]	18 (10)	38 (21)
Accidental injury	12 (7)	19 (10)
Asthenia	12 (7)	10 (5)
Back pain	9 (5)	6 (3)
Chest pain	1 (<1)	4 (2)
Fever	8 (4)	7 (4)
Flu syndrome	8 (4)	12 (7)
Headache	62 (35)	63 (35)
Infection	15 (8)	11 (6)
Pain	9 (5)	11 (6)
Cardiovascular system		
Tachycardia	1 (<1)	4 (2)
Digestive system		
Anorexia	4 (2)	13 (7)
Constipation	2 (1)	5 (3)
Diarrhea	13 (7)	7 (4)
Dry mouth	5 (3)	8 (4)
Dyspepsia	6 (3)	11 (6)
Nausea	15 (8)	30 (16)
Vomiting	9 (5)	14 (8)
Hemic and lymphatic system		
Ecchymosis	2 (1)	4 (2)
Metabolic and nutritional		
Weight loss	0	4 (2)
Musculoskeletal system		
Arthralgia	4 (2)	4 (2)
Myalgia	1 (<1)	5 (3)

Nervous system		
Dizziness	11 (6)	21 (12)
Emotional lability[c]	0	4 (2)
Hostility	2 (1)	7 (4)[d]
Hyperkinesia	5 (3)	4 (2)
Insomnia	10 (6)	18 (10)
Nervousness	9 (5)	13 (7)
Somnolence	9 (5)	9 (5)
Suicidal ideation	0	6 (3)
Tremor	1 (<1)	6 (3)
Respiratory system		
Cough increased	5 (3)	7 (4)
Epistaxis	2 (1)	9 (5)
Pharyngitis	19 (11)	19 (10)
Rhinitis	18 (10)	13 (7)
Upper respiratory infection	9 (5)	13 (7)
Skin and appendages		
Rash	5 (3)	7 (4)
Special senses		
Ear pain	4 (2)	5 (3)
Mydriasis	1 (<1)	8 (4)
Urogenital system		
Dysmenorrhea[e]	7 (8)	8 (10)
Adverse event associated with miscellaneous factors		
Allergic reaction other than drug	11 (6)	9 (5)

Abbreviations: TEAEs = treatment-emergent adverse events.

a: Includes patient 394-0924, who had 1 on-therapy adverse event of clinical interest that was discovered after the database was locked, and was added by an erratum.

b: Adverse events in italics are those that occurred more often with venlafaxine ER than placebo.

c: Mostly "crying."

d: Includes reports for patients 394-0924 and 394-1089 of hostility (verbatim terms aggressive outburst and rage, respectively). These adverse events were discovered after the database was locked, and were added by errata.

e: Percentage adjusted for the number of girls (placebo-controlled studies: venlafaxine ER, n = 80; placebo, n = 86).

12. MDD: Selected Mean Laboratory Studies

TABLE 2.7.2A. SELECTED MEAN LABORATORY RESULTS—DEPRESSION STUDIES

	Placebo-controlled Studies							All 3 Studies		
	Placebo			Venlafaxine ER				Venlafaxine ER		
Parameter Time Interval	n	Baseline Mean	Mean Change	n	Baseline Mean	Mean Change	ER vs Pbo[a] p-Value	n	Baseline Mean	Mean Change
AST/SGOT, U/L										
Month 2	117	24.0	1.4*	113	24.0	1.9**		125	23.8	2.6**
Month 3	--	--	--	--	--	--		53	24.1	0.3
Month 6	--	--	--	--	--	--		31	23.9	0.0
Final on-therapy	137	23.9	1.1*	135	24.0	1.5**		208	24.1	1.1*
Poststudy[b]	27	25.6	1.1	22	23.9	1.4		45	24.2	0.5
Alkaline phosphatase, mmol/L										
Month 2	114	202.8	-5.0	114	211.2	-9.6**		127	209.3	-8.9**
Month 3	--	--	--	--	--	--		53	195.4	-9.5
Month 6	--	--	--	--	--	--		31	196.0	-12.0*
Final on-therapy	134	198.8	-3.3	137	211.7	-11.5***		208	205.6	-11.0***
Poststudy[b]	26	210.2	5.5	22	235.0	-9.9		45	214.2	-16.1**
Total cholesterol,[c] mmol/L										
Month 2	117	4.30403	-0.11339**	114	4.20474	0.01247		127	4.19502	0.02565
Month 3	--	--	--	--	--	--		54	4.11653	0.05436
Month 6	--	--	--	--	--	--		32	3.99375	0.08728
Final on-therapy	137	4.29899	-0.09948*	138	4.23279	0.01293		211	4.20966	0.00601
Poststudy[b]	22	4.53137	-0.28857	14	4.25766	0.00647		35	4.10287	-0.00850
Glucose,[c] mmol/L										
Month 2	113	5.03	-0.04	109	5.03	-0.13		123	5.01	-0.11
Month 3	--	--	--	--	--	--		51	5.05	-0.01
Month 6	--	--	--	--	--	--		31	5.00	-0.13
Final on-therapy	133	5.01	-0.03	131	5.01	-0.10		202	4.99	-0.05
Poststudy[b]	27	4.90	0.03	20	5.15	0.0		41	5.04	-0.01

TABLE 2.7.2A. SELECTED MEAN LABORATORY RESULTS—DEPRESSION STUDIES

	Placebo-controlled Studies							All 3 Studies		
	Placebo			Venlafaxine ER				Venlafaxine ER		
Parameter Time Interval	n	Baseline Mean	Mean Change	n	Baseline Mean	Mean Change	ER vs Pbo[a] p-Value	n	Baseline Mean	Mean Change
Total protein, g/L										
Month 2	117	74.80	-1.49***	114	74.90	-0.97*		126	75.06	-0.86*
Month 3	--	--	--	--	--	--		54	74.85	-0.36
Month 6	--	--	--	--	--	--		31	74.84	-0.87
Final on-therapy	137	74.91	-1.54***	137	74.69	-1.01**		210	74.57	-0.99**
Poststudy[b]	27	75.33	-1.30	22	75.86	-1.39		45	75.20	-1.62*

Abbreviations: Abbreviations: AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; BUN = blood urea nitrogen; ER = venlafaxine ER; Pbo = placebo, -- = no assessments at that time point in the short-term studies.

a: Comparisons of adjusted mean changes from baseline between the venlafaxine ER and placebo treatment groups in the pooled placebo-controlled studies are provided if significant ($p \leq 0.05$).

b: The poststudy period was defined as the period beginning 3 days after the last dose of study medication, regardless of the duration of treatment.

c: Not fasting.

*, **, ***: Significantly different from baseline at the 0.05, 0.01, and 0.001 levels, respectively.

TABLE 2.7.2A. SELECTED MEAN LABORATORY RESULTS—DEPRESSION STUDIES

Parameter / Time Interval	Placebo-controlled Studies: Placebo n	Placebo Baseline Mean	Placebo Mean Change	Venlafaxine ER n	Venlafaxine ER Baseline Mean	Venlafaxine ER Mean Change	ER vs Pbo[a] p-Value	All 3 Studies: Venlafaxine ER n	Venlafaxine ER Baseline Mean	Venlafaxine ER Mean Change
Sodium, mmol/L										
Month 2	117	141.0	0.0	114	141.1	-0.3		127	141.1	-0.3
Month 3	--	--	--	--	--	--		53	140.6	1.1
Month 6	--	--	--	--	--	--		30	140.7	1.4
Final on-therapy	137	140.9	0.1	137	141.0	-0.3		209	140.9	0.1
Poststudy[b]	27	141.0	-0.5	20	141.0	-0.2		43	140.5	0.1
Chloride, mmol/L										
Month 2	117	104.3	0.2	114	104.4	-0.4		126	104.3	-0.2
Month 3	--	--	--	--	--	--		53	103.9	1.4**
Month 6	--	--	--	--	--	--		30	104.0	1.6**
Final on-therapy	137	104.2	0.3	137	104.4	-0.5*	0.030	209	104.2	0.1
Poststudy[b]	27	103.2	0.1	20	104.3	-1.1		43	104.1	-0.2
BUN, mmol/L										
Month 2	117	4.345	-0.104	114	4.268	0.041		126	4.233	0.074
Month 3	--	--	--	--	--	--		54	4.099	0.271
Month 6	--	--	--	--	--	--		32	4.340	-0.234
Final on-therapy	137	4.396	-0.078	137	4.287	-0.003		210	4.260	-0.019
Poststudy[b]	27	4.324	0.099	21	4.250	0.255		44	4.300	0.016
Creatinine, µmol/L										
Month 2	71	52.0	0.2	70	55.1	-0.9		82	55.1	-0.6
Month 3	--	--	--	--	--	--		54	52.5	1.9
Month 6	--	--	--	--	--	--		32	51.9	2.8
Final on-therapy	79	53.8	-0.3	80	54.0	-1.0		153	53.7	0.2
Poststudy[b]	14	49.9	2.8	14	56.2	0.0		37	55.7	0.5

13.

Subjects With Clinically Important Laboratory Results-MDD

TABLE 2.7.1.2A. PATIENTS WHO HAD CLINICALLY IMPORTANT LABORATORY TEST RESULTS—DEPRESSION STUDIES

Treatment Group / Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg)	Days on Therapy at Onset	Finding
Venlafaxine ER				
394-0921	15/M	70.9	56	ALT/SGPT increased; AST/SGOT increased[b,c]
394-1682	16/F	167.8	60	ALT/SGPT increased; AST/SGOT increased[c]
395-0160	8/F	92.3	63	Eosinophils increased[b,c]
395-0543	12/F	100.1	57	Elevated ALT/SGPT[c,d]
Placebo				
38209-006	15/M	N/A	63	Decreased white blood cell count[b,c]
394-0321	7/M	N/A	55	AST/SGOT increased[b,c]
394-1086	11/M	N/A	54	ALT/SGPT increased; AST/SGOT increased[b,c]

Abbreviations: ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase
a: Age at baseline.
b: Also reported as an adverse event.
c: Values outside the age/sex-specific normal laboratory ranges.
d: Values met Wyeth criteria for potential clinical importance.
N/A = not applicable.

14. Subjects With Clinically Important ECG Results In MDD

TABLE 2.9.1.2A. PATIENTS WHO HAD CLINICALLY IMPORTANT ECG RESULTS—DEPRESSION STUDIES

Treatment Group Patient Number	Age[a] (y)/Sex	Mean Daily Dose (mg)	Days on Therapy at Onset	Finding
Venlafaxine ER				
38211-021	11/M	77.6	42	Pre-excitation syndrome[b,c]
394-0448	9/F	70.6	59	Low right atrial rhythm[c]
394-0602	11/M	124.8	64	First-degree A-V block[c]
395-0350	13/F	120.8	154	Rightward axis[c,d]
395-0384	10/M	78.6	179	Low right atrial rhythm[c]
Placebo				
38202-022	12/M	N/A	56 (poststudy)[e]	Marked bradycardia[c,f]
38207-013	13/M	N/A	59	ST elevation and consider early repolarization[c]
38209-012	8/M	N/A	42	Voltage criteria for left ventricular hypertrophy[c]
394-0135	10/F	N/A	14 (poststudy)	Sinus arrhythmia and borderline prolonged QT[c]
394-0846	16/F	N/A	58	Sinus bradycardia[c,d]

Abbreviation: N/A = not applicable.
a: Age at baseline.
b: One (1) month after the poststudy visit, consultation with another cardiologist confirmed that the condition had been present prestudy. Also reported as an adverse event (supraventricular tachycardia).
c: Values met the Wyeth criteria for potentially clinically important result (overall evaluation not normal).
d: Also reported as an adverse event.
e: Bradycardia was first reported on day 42, but did not reach criterion for a potentially clinically important change until poststudy.
f: Values outside age/sex-specific normal range criteria for heart rate.

15. Serious Adverse Events in GAD

TABLE 3.12.2A. LISTING OF PATIENTS WITH SERIOUS ADVERSE EVENTS—GAD STUDIES

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term	Discontinuation Because of Adverse Event[c]
Venlafaxine ER							
Body as a whole							
396-0704[d]	10/F	57.3	1.69	0	54[e]	Withdrawal syndrome	No
Nervous system							
396-0704[d]	10/F	57.3	1.69	0	54[e]	Agitation, confusion	No
397-0361	10/M	70.6	1.04	0	19[e]	Suicidal ideation	Yes
Placebo							
Body as a whole							
396-0863[d]	11/M	N/A	N/A	N/A	3	Infection (mononucleosis)	Yes
397-0012	17/F	N/A	N/A	N/A	15[e]	Suicide attempt, overdose	Yes
Cardiovascular system							
396-0863[d]	11/M	N/A	N/A	N/A	4	Hypotension	No
Metabolic and nutritional							
396-0863[d]	11/M	N/A	N/A	N/A	4	Dehydration	No

Abbreviation: N/A = not applicable.
a: Age at baseline.
b: Calculated by using baseline weight.
c: Discontinuation due to listed serious adverse event.
d: Patient listed in table more than once because he or she had serious adverse events in more than 1 body system category
e: Onset of adverse event was 1 or more days after the last *full* dose of study medication. Patient 396-0704: 1 day for both events; 397-0361: 2 days; 397-0012: 1 day.

16. Adverse Events of Clinical Interest in GAD

TABLE 3.12.3A. LISTING OF PATIENTS WITH OTHER ADVERSE EVENTS OF CLINICAL INTEREST—GAD STUDIES

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term[c]	Discontinuation Because of Adverse Event
Venlafaxine ER							
Body as a whole							
396-0540	16/M	123.1	1.73	0	64[d]	Abdominal pain	Yes[e]
396-1102	13/M	108.1	2.07	150.0	34	Flu syndrome	Yes
396-1380[f]	7/M	53.5	1.76	0	56 (poststudy)[d]	Discontinuation symptoms	No
397-0084[f]	6/M	51.1	1.41	75.0	22	Abdominal pain	Yes
Cardiovascular system							
396-1704	10/M	104.5	2.40	112.5	28	Hypertension	No
397-0693	10/M	37.5	1.10	37.5	14	Hypertension	No
Digestive system							
397-0701[f]	15/F	127.9	2.43	75.0	64 (taper)	Nausea	Yes[e]
Metabolic and nutritional							
396-1702	8/M	87.7	2.76	75.0	28	Weight loss	No
397-0487[f]	10/M	111.2	1.35	150	56	Hypercholesterolemia	No
397-0690	16/F	165.1	2.62	75	14	Weight loss	No
397-0701[f]	15/F	127.9	2.43	150	28	Weight loss	No
Nervous system							
396-1380[f]	7/M	53.5	1.76	75.0	29	Abnormal/changed behavior (oppositional defiant behavior)	Yes
396-1540	12/F	98.7	2.28	187.5	14	Neuritis	Yes
397-0005	10/F	82.8	2.53	112.5	43	Agitation	No
397-0016	16/F	32.1	0.29	37.5	6	Agitation	No
397-0084[f]	6/M	51.1	1.41	37.5	4	Hostility (aggressiveness)	No
				75.0	22	Paranoid reaction, thinking abnormal (difficulty concentrating)	Yes

TABLE 3.12.3A. LISTING OF PATIENTS WITH OTHER ADVERSE EVENTS OF CLINICAL INTEREST—GAD STUDIES

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term[c]	Discontinuation Because of Adverse Event
397-0361	10/M	70.6	1.04	0	19[d]	Abnormal/changed behavior (acting out)	Yes
				0	20[d]	Hostility (aggressive behavior)	No
397-0487[f]	10/M	111.2	1.35	150.0	38	Hostility (violent outburst)	No
397-0701[f]	15/F	127.9	2.43	75.0	64 (taper)	Nervousness	Yes[e]
397-0764	6/F	64.3	2.29	75.0	36	Abnormal/changed behavior (impulsive)	No
Placebo							
Body as a whole							
396-1627	15/M	N/A	N/A	N/A	12	Neoplasm (lump in suprascapular region)	No
397-0008	13/F	N/A	N/A	N/A	41	Abdominal pain	Yes
397-0041	13/F	N/A	N/A	N/A	prestudy	Abdominal pain	Yes
397-0486[f]	8/F	N/A	N/A	N/A	1	Headache	Yes
397-0761	9/M	N/A	N/A	N/A	4	Fever	No
Cardiovascular system							
396-0308[f]	9/M	N/A	N/A	N/A	7	Hypertension	No
397-0486[f]	8/F	N/A	N/A	N/A	14	Hypertension	No
397-0697	14/M	N/A	N/A	N/A	16	Hypertension	No
Digestive system							
396-0308[f]	9/M	N/A	N/A	N/A	44	Fecal incontinence	No
396-0826	11/M	N/A	N/A	N/A	56	Liver function tests abnormal	No
397-0575	8/F	N/A	N/A	N/A	6	Gastritis	Yes
397-0695	8/M	N/A	N/A	N/A	24	Fecal incontinence	No
Metabolic and nutritional							
397-0691	7/M	N/A	N/A	N/A	7	Weight gain	No
397-0801	17/M	N/A	N/A	N/A	4	Weight gain	No

Treatment *Body System* Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg/day)	Mean Daily Dose (mg/kg/day)[b]	Total Daily Dose at Onset (mg/day)	Study Day at Onset	Adverse Event Preferred Term[c]	Discontinuation Because of Adverse Event
Nervous system							
396-1622	11/M	N/A	N/A	N/A	10	Nervousness (increased irritability)	Yes
397-0012	17/F	N/A	N/A	N/A	16[d]	Dizziness	Yes
397-0017	8/M	N/A	N/A	N/A	8	Hyperkinesia	Yes
397-0689	17/F	N/A	N/A	N/A	48	Nervousness (increased irritability)	Yes
397-1401	10/M	N/A	N/A	N/A	9	Agitation	No

Abbreviation: N/A = not applicable.
a: Age at baseline.
b: Calculated by using baseline weight.
c: Verbatim terms are included in parentheses for vague COSTART terms.
d: Onset of adverse event was 1 or more days after the last *full* dose of study drug. 396-0540: 1 day; 396-1380: 2 days; 397-0361: 2 days for abnormal/changed behavior, 3 days for hostility; 397-0012: 2 days.
e: Patient discontinued during the taper period.
f: Patient listed in table more than once because of the occurrence of adverse events of clinical interest in more than 1 body system category

17. Most Common TEAE's in 2 % Venlafaxine ER Subjects in GAD

TABLE 3.6.1.1A. COMMON TEAEs (≥2% IN THE VENLAFAXINE ER GROUP) DURING THE ON-THERAPY PERIOD: NUMBER (%) OF PATIENTS—GAD STUDIES

Body System Adverse Event	Placebo (n = 163)	Venlafaxine ER (n = 157)
Any adverse event	131 (80)	123 (78)
Body as a whole		
Abdominal pain	27 (17)	26 (17)
Accidental injury[a]	15 (9)	18 (11)
Asthenia	6 (4)	13 (8)
Chest pain	2 (1)	4 (3)
Fever	10 (6)	6 (4)
Flu syndrome	5 (3)	5 (3)
Headache	55 (34)	38 (24)
Infection	22 (13)	6 (4)
Pain	5 (3)	11 (7)
Cardiovascular system		
Vasodilatation	0	4 (3)
Digestive system		
Anorexia	5 (3)	20 (13)
Diarrhea	12 (7)	13 (8)
Dry mouth	2 (1)	6 (4)
Dyspepsia	4 (2)	7 (4)
Gastroenteritis	3 (2)	4 (3)
Nausea	14 (9)	17 (11)
Vomiting	11 (7)	13 (8)
Metabolic and nutritional		
Weight loss	2 (1)	5 (3)
Musculoskeletal system		
Myalgia	2 (1)	6 (4)
Nervous system		
Agitation	2 (1)	5 (3)
Dizziness	4 (2)	7 (4)
Hyperkinesia	2 (1)	5 (3)
Insomnia	8 (5)	8 (5)
Nervousness	4 (2)	7 (4)
Somnolence	4 (2)	11 (7)
Thinking abnormal	2 (1)	5 (3)
Respiratory system		
Cough increased	13 (8)	8 (5)
Epistaxis	9 (6)	7 (4)
Pharyngitis	18 (11)	14 (9)
Rhinitis	15 (9)	8 (5)
Upper respiratory infection	7 (4)	12 (8)
Skin and appendages		
Contact dermatitis	2 (1)	4 (3)
Rash	5 (3)	4 (3)
Sweating	2 (1)	5 (3)

Body System Adverse Event	Placebo (n = 163)	Venlafaxine ER (n = 157)
Special senses		
Mydriasis	1 (<1)	3 (2)
Urogenital system		
Dysmenorrhea[b]	9 (12)	4 (7)
Adverse event associated with miscellaneous factors		
Allergic reaction other than drug	8 (5)	5 (3)

Abbreviation: TEAEs = treatment-emergent adverse events.
a: Adverse events in italics are those that occurred more often with venlafaxine ER than placebo.
b: Percentage adjusted for the number of girls (venlafaxine ER, n = 58; placebo, n = 78.).

18. Subjects With Clinically Important Laboratory Results-GAD

TABLE 3.7.1.2A. PATIENTS WHO HAD CLINICALLY IMPORTANT LABORATORY TEST RESULTS-GAD STUDIES

Treatment Group Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg)	Days on Therapy at Onset	Finding
Venlafaxine ER				
397-0487	10/M	111.2	56	Elevated cholesterol[b,c,d]
Placebo				
396-0154	12/M	N/A	64	Elevated ALT/SGPT and AST/SGOT[c,e]
396-0826	11/M	N/A	56	Elevated ALT/SGPT and AST/SGOT[b,c]
396-0863	11/M	N/A	35 (poststudy)	Elevated ALT/SGPT and AST/SGOT[b,c]

Abbreviations: ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; N/A = not applicable.
a: Age at baseline.
b: Also reported as an adverse event.
c: Values outside the age/sex-specific normal laboratory ranges.
d: The patient had a history of hypercholesterolemia.
e: Values met Wyeth criteria for potential clinical importance.

19. Subjects With Clinically Important ECG Results-GAD

TABLE 3.9.1.2A. PATIENTS WHO HAD CLINICALLY IMPORTANT ECG RESULTS—GAD STUDIES

Treatment Group Patient Number	Age[a] (y)/ Sex	Mean Daily Dose (mg)[b]	Days on Therapy at Onset	Finding
Venlafaxine ER				
396-0300	6/M	101.7	59	Right atrial rhythm abnormal[b]
397-0006	16/M	168.8	56	Sinus rhythm with sinus tachycardia[b]
397-0007	16/F	165.5	58	Normal sinus rhythm with short PR interval[b]
397-0564	14/M	98.0	57	Left atrial rhythm, rightward axis, and nonspecific ST abnormality[b]
Placebo				
397-0685	10/F	N/A	8	First-degree atrioventricular block[b]

Abbreviation: N/A = not applicable.
a: Age at baseline.
b: Values met the Wyeth criteria for potentially clinically important results (overall interpretation not normal).

20. Subgroup Analysis For Interaction of Age/Sex Factor and CDRS-R in MDD:

TABLE 2.4.3B. POOLED DATA FOR STUDIES B1-382 (EXCLUDING SITE 38209) AND B1-394 BY AGE AND SEX – FINAL ON-THERAPY ADJUSTED MEAN CHANGES FROM BASELINE FOR THE CDRS-R TOTAL SCORE: ITT PATIENTS AND LOCF ANALYSIS

Boys		Girls	
Children			
Placebo (n = 56)	Ven ER (n = 56)	Placebo (n = 36)	Ven ER (n = 37)
-23.7	-22.0	-20.3	-21.6
Adolescents			
Placebo (n = 28)	Ven ER (n = 40)	Placebo (n = 45)	Ven ER (n = 36)
-14.7	-20.4	-17.4	-24.8

p-Values		
Age/Sex[a]	Therapy[a]	Interaction[b]
0.041	0.091	0.324

Abbreviations: Ven ER = venlafaxine ER.
a: Model B was used.
b: Model A was used.

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/s/

Glenn Mannheim
2/25/03 03:00:17 PM
MEDICAL OFFICER

Paul Andreason
2/28/03 12:00:56 PM
MEDICAL OFFICER
I agree with Dr Mannheim that the supplement is not approveable. Please refer to my memo to the file.