Clinical Review for NDA 20-151 Supplement SE5-024

Non-Approval Action for Pediatric Supplement for Effexor XR; negative results for Effexor XR in the treatment of Major Depressive Disorder (MDD and negative trial in Effexor XR in the treatment of Generalized Anxiety Disorder) in pediatric patients

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The original supplement for the expanded indications of the treatment of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) in children and adolescents was submitted September 25, 2002 as Supplement SE5-024 to NDA 20-151. Two of two studies of MDD failed to provide evidence of efficacy over placebo. Only one of two studies provided convincing evidence of efficacy over placebo in the treatment of GAD**.** It is my view that none of the efficacy results of this negative program for venlafaxine in pediatric MDD and GAD should be noted in labeling. However, there are safety findings of decreased weight gain and growth with venlafaxine use in this pediatric sample and I recommend that they should be added to labeling.

I recommend that the sponsor pool the four, 8-week, placebo controlled studies of MDD and GAD combined and look at the mean changes in weight and height in the venlafaxine treated patients versus the placebo treated patients.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Effexor and Effexor XR are combination serotonin and norepinephrine reuptake inhibitors that are approved for the treatment of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) in adults. This supplement was submitted in support of pediatric labeling for Effexor XR in the treatment of MDD and GAD. This supplement presents the results of four studies: two studies in support of a claim for GAD and two in support of a claim for MDD. The MDD studies individually fail to provide evidence that Effexor XR is effective in the treatment of MDD in pediatric patients. Although one of two clinical trials did not individually support the efficacy of Effexor XR in the treatment of GAD, the sponsor proposed that the indication might be approved on the basis of one study.

It should also be noted that the sponsor had sought pediatric exclusivity for this program under FDAMA, and they are given 6 months of additional exclusivity based on the fact that they conducted the studies required under the Written Request. The Written Request stipulated that two positive studies were required to support a claim for MDD and GAD.

Since the proposal was to use the currently approved Effexor XR formulations for this expanded population, there was no need for chemistry or pharmacology reviews. Glenn Mannheim, MD did the primary review of the clinical efficacy and safety data from the clinical group. Fanhui Kong, PhD, from biometrics, also reviewed the efficacy data. Ron Kavanagh, PhD, reviewed the pediatric pharmacokinetic data.

There are two pharmacokinetic studies of venlafaxine in the pediatric population; one is done with the IR formulation (126-US) and one is done with the ER formulation (169-US). 126-US was a multiple dose study and 169-US was a single dose PK study. Dr Kavanagh pointed out that dose normalized AUCs are lower in adolescents than in adults and even lower in preadolescents and younger children. Therefore, Dr. Kavanagh concluded that children, depending on age, might need a 2-4 fold higher dose on a mg/kg/basis as compared to adults. Adolescents needed only a slightly higher mg/kg/dose as compared to adults to achieve equivalent exposures (with the caveat that the exposures to the active metabolites, NDV and NODV, were not considered). However, because effectiveness has not been demonstrated, we will not add pharmacokinetic data for pediatric patients to labeling.

B. Efficacy

Summary of Studies of MDD

Two, 8-week, multi-center parallel group randomized, double blind, placebo controlled flexible dose studies did not provide any evidence of venlafaxine's efficacy in the treatment of MDD in children. These studies employed doses ranging from 37.5 to 225-mg/day. They were adequately powered studies with 161 (103 completing) patients in study 382 and 193 patients (143 completing) in study 394. There were no differences between placebo and drug treatment groups at week eight (8) via the last-observation-carried-forward (LOCF) on-therapy evaluation (382: P=0.338; 394: P=0.386).

Summary of Studies of GAD

The sponsor submitted the results of two 8-week, double blind, placebo controlled, parallel group, flexible dose studies of children aged 6-17 years. Effexor XR demonstrated efficacy in only one of two studies (397-US).

Study 396-US did not separate Effexor XR treatment from placebo at any time point. The following table (Table 9.4.1A) from the sponsor's report shows that there was no time point at which the two treatment groups were significantly different. This difference from study 397-US is difficult to explain. Potential explanations for study failure such as differences in mean ages, placebo responses, drop-out rates, and mean daily doses, were nearly identical across the studies. In the end, drug effect was markedly different between the two studies with a mean adjusted venlafaxine change from baseline in 396-US of -15.5 and in 397-US of -18.7. Treatment separation from placebo was statistically significant starting at week 2 in study 397-US and generally speaking became stronger over the duration of the study. This was not the case in Study 396-US.

Study 396-US Primary Efficacy Variable Analysis Summary

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)	

Study 397-US Primary Efficacy Variable Analysis Summary

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

Conclusions Regarding Efficacy Data

Given the pediatric PK data, under dosing is a tempting hypothesis to entertain for the reason of the failure of study 396-US in GAD; however, the mean age and mean mg/kg dose across studies 396-US and 397-US are nearly identical. This therefore argues against under dosing alone as an explanation for this inconsistency.

Under dosing likewise is probably not the most likely explanation for the failure of the MDD pediatric studies with Effexor XR. Development programs for MDD in children with the exception of fluoxetine are failing even with adequate dosing. This is not the case with OCD. This is even more mysterious given that in adults only about half the doses of SSRIs that are required to treat Panic, OCD and Social Phobia are necessary to treat MDD.

There are no drugs approved for the treatment of GAD in children. Therefore, it is difficult to say whether or not the treatment response of pediatric patients with GAD will behave more like OCD or MDD. In the tricyclic antidepressant (TCA) era, off-label use of TCAs in the treatment of panic disorder was common but there did not seem to be much utility in using these drugs for GAD. OCD did not respond to TCAs in general with the one exception being clomipramine.

Most people would not have predicted the lack of efficacy of SSRI (and now venlafaxine) antidepressant treatments in children given the experience in adults. This lack of predictability and the historical lack of uniformity in treatment response across the anxiety disorders as a group leads me not to endorse the approval of a pediatric indication for GAD based on one positive study and positive results in adults. Though ultimately with experience it may prove to be sufficient evidence for efficacy, there is not enough experience at this point with GAD for me to come to that conclusion.

C. Safety

The pediatric safety of venlafaxine was explored in four placebo controlled 8-week studies (two in MDD and Two in GAD) and one open label extension study of MDD. One other 6-week phase I-II study of Conduct disorder (Study 126) was included in the sponsor's review of the safety. Thus 339 patients were exposed to Effexor XR in the four 8-week placebo controlled studies and 86 MDD patients received Effexor XR for up to 6-months. This represents 52.2 patient-years of exposure in patients with MDD and GAD.

The safety profile of venlafaxine ER in children and adolescents appears to be generally comparable to the safety profile in adults with some differences. The mean increase from baseline in the total serum cholesterol was higher than adults in the pooled GAD, but, not in the pooled MDD trials. A slightly higher mean pulse rate and ECG heart rate in children and adolescents than in adults was seen. Increases in blood pressure in children were of similar magnitude with adults.

In the pediatric population, a smaller increase in height in children in the pooled GAD studies versus placebo was noted. This was not noted in the MDD group; however, it is surprising that this was noted at all in an 8-week study period. Though height was significantly increased from baseline after 8 weeks of treatment for both venlafaxine ER- treated and placebo- treated patients, the adjusted mean increase at month 2 in the placebo group (1.3 cm) was significantly greater than the venlafaxine ER group (0.4 cm). Mean height in the long term open label treated patients only increased 1.2-cm over 6-months.

Both MDD and GAD patients treated with venlafaxine had mean decreases in weight. The mean weight losses were 0.5 kg (MDD) and 0.6 kg (GAD) over an 8-week period while there was a mean weight gain in the placebo treated MDD and GAD patients. Weight changes in both MDD and GAD patients were statistically significant.