



Pfizer Global Pharmaceuticals

November 30, 2006

RE:

**DOCKET: 2006N-0414 –“SUICIDALITY DATA FROM ADULT ANTIDEPRESSANT TRIALS”
ZOLOFT® (SERTRALINE HYDROCHLORIDE) TABLETS & ORAL CONCENTRATE
BACKGROUND PACKAGE FOR DECEMBER 13 ADVISORY COMMITTEE**

Dear Advisory Committee members,

Reference is made to the December 13, 2006, FDA Advisory Committee which will examine suicidality data from adult antidepressant trials. With this correspondence Pfizer is submitting additional data and analysis that it has conducted.

FDA requested analysis

On December 24th, 2004, FDA sent Pfizer a request for an evaluation of “Possibly Suicide-Related” adverse events for Zoloft (sertraline hydrochloride) in adult patients with Major Depressive Disorder (MDD). The algorithm for identifying “Possibly Suicide-Related” Adverse Events was stipulated by FDA, and the study inclusion criteria delineated by FDA was placebo-controlled, short-term (up to 17 weeks) MDD trials with at least 30 patients. Additionally, FDA requested that the search should be limited to events occurring during the double-blind phase of the treatment, or within 1 day of stopping randomized treatment. Subsequent to the original request, on May 12, 2005, FDA requested that the search for “possibly suicide-related” adverse events be broadened from MDD trials to trials for all indications (non-MDD) studied for Zoloft with the same criteria as the original request. A complete set of narrative summaries were prepared for these cases. All identified events were classified by two psychiatrists who were blinded to the subject treatments using the Columbia classification coding system as stipulated by the Agency. The coding scheme used (as stipulated by the agency) was as follows:

FDA Classification Codes	
Code	Description
1	Completed suicide
2	Suicide attempt
3	Preparatory acts toward imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information (fatal)
7	Self-injurious behavior, no suicidal intent
8	Other: accident, psychiatric, medical
9	Not enough information (nonfatal)

Results of the FDA requested MDD and non-MDD analysis

The total of 75 (19 MDD and 56 non-MDD) studies with 13,345 adult patients were included in the analysis (6,561 treated with sertraline, 5,480 treated with placebo, and 1,304 treated with another active control agent). Results are shown in Table 1 below:

Table 1. NUMBER OF SUBJECTS WITH POSSIBLY SUICIDE RELATED ADVERSE EVENTS IN A TOTAL OF 13,345 ADULT PATIENTS IN 75 PLACEBO-CONTROLLED, SHORT-TERM COMPLETED STUDIES OF SERTRALINE IN MDD AND INDICATIONS OTHER THAN MDD (NON-MDD)			
Code	Sertraline (N=6,561)	Placebo (N=5,480)	Active control agent (N=1,304)
Completed suicide (Code 1)	0	1	0
Suicide attempt (Code 2)	6	7	5 (2 in clomipramine-, 2 in imipramine- and 1 in desipramine-treated subjects)
Preparatory acts toward imminent suicidal behavior (Code 3)	1	1	1 (in an imipramine- treated subject)
Suicidal ideation (Code 4)	13	20	4 (2 in clomipramine- and 2 in imipramine-treated subjects)
Self-injurious behavior, intent unknown (Code 5)	3	1	0
Not enough information (fatal) (Code 6)	0	0	0
Self-injurious behavior, no suicidal intent (Code 7)	0	0	0
Other: accident; psychiatric; medical (Code 8)	79	83	16
Not enough information (nonfatal) (Code 9)	7	6	3

N = number of patients treated

The results of the adult short-term placebo-controlled clinical trials of sertraline, compiled in accordance with an FDA-specified search strategy, show no increased risk of suicidal thinking or behavior in sertraline-treated patients versus those treated with placebo. Also, please note that these results were presented as a poster at APA in May 2006.

Additional data and analysis

Subsequent to the FDA requested analysis, Pfizer conducted an additional, larger analysis that included adult Zoloft short and long-term, completed, placebo-controlled, Phase 2-4 trials. We used the same FDA specified search algorithm for “Possibly Suicide-Related” Adverse Events, and our search was limited to events occurring during the double-blind phase of the treatment, or within 30 days of stopping randomized treatment. No narratives were prepared for additional cases identified. All events were classified by two psychiatrists who were blinded to the subject treatments for the identified cases using the Columbia classification coding system as was used in the FDA requested analysis.

Results of the additional analysis

A total of 126 studies across all indications with 22,057 patients were included in the analysis (10,923 treated with sertraline, 9,006 treated with placebo, and 2,128 treated with another active control agent). The incidence rates, unadjusted for duration of exposure, of the results are shown in Table 2.

Table 2. SUMMARY OF INCIDENCE IN SERTRALINE COMPLETED, PLACEBO-CONTROLLED, ADULT PHASE 2 – 4 STUDIES (UNADJUSTED FOR EXPOSURE)						
Code	Sertraline (N=10923)		Placebo (N=9006)		Sertraline vs. Placebo	
	n (%) 95% CI	n (%) 95% CI	Relative Risk	95% CI (Lower, Upper)		
Completed suicide (Code 1)	4 (0.04) (0.01, 0.09)	3 (0.03) (0.01, 0.10)	1.10	(0.246, 4.911)		
Suicide attempt (Code 2)	24 (0.22) (0.14, 0.33)	11 (0.12) (0.06, 0.22)	1.80	(0.882, 3.670)		
Preparatory acts toward imminent suicidal behavior (Code 3)	2 (0.02) (0.00, 0.07)	2 (0.02) (0.00, 0.08)	0.82	(0.116, 5.852)		
Suicidal ideation (Code 4)	28 (0.26) (0.17, 0.37)	29 (0.32) (0.22, 0.46)	0.80	(0.474, 1.337)		
Self-injurious behavior, intent unknown (Code 5)	7 (0.06) (0.03, 0.13)	1 (0.01) (0.00, 0.06)	5.77	(0.710, 46.901)		
Not enough information (fatal) (Code 6)	3 (0.03) (0.01, 0.08)	0 (0.00)	-----	-----		
Self-injurious behavior, no suicidal intent (Code 7)	0 (0.00)	0 (0.00)	-----	-----		
Other: accident; psychiatric; medical (Code 8)	188 (1.72) (1.49, 1.98)	147 (1.63) (1.38, 1.92)	1.05	(0.851, 1.306)		
Not enough information (nonfatal) (Code 9)	64 (0.59) (0.45, 0.75)	40 (0.44) (0.32, 0.60)	1.32	(0.890, 1.956)		

N = number of patients treated

n = number of patients having an event

In light of the fact that long-term trials were included in this analysis, we also calculated exposure-adjusted results. These results are shown below in Table 3. Please note that 12 studies (with 11 identifiable events) are not included in this analysis due to duration data not being available. These studies are as follows: 89CE21-0457, N-0254, N-0255, N-0256, N-0325, N-0355, N-0359, STL-CR-90-002, STL-JP-93-603, STL-JP-94-601, STL-JP-94-603, and STL-JP-94-604. Generally, the double-blind phase was used for relapse prevention studies except for 1 study (STL-UK-91-002), which may have information from the open-label phase of sertraline exposure included.

Table 3. SUMMARY OF EXPOSURE-ADJUSTED RATES IN SERTRALINE COMPLETED, PLACEBO-CONTROLLED, ADULT PHASE 2 – 4 STUDIES

Code	Sertraline n/person-years (rate)	Placebo n/person-years (rate)	Sertraline vs. Placebo	
			Relative Rate	95% CI (Lower, Upper)
Completed suicide (Code 1)	3/2897 (0.001)	3/2306 (0.001)	0.80	(0.161, 3.940)
Suicide attempt (Code 2)	20/2897 (0.007)	10/2306 (0.004)	1.59	(0.747, 3.394)
Preparatory acts toward imminent suicidal behavior (Code 3)	1/2897 (0.0003)	2/2306 (0.001)	0.40	(0.036, 4.387)
Suicidal ideation (Code 4)	26/2897 (0.009)	28/2306 (0.012)	0.74	(0.435, 1.257)
Self-injurious behavior, intent unknown (Code 5)	6/2897 (0.002)	1/2306 (0.0004)	4.78	(0.575, 39.642)
Not enough information (fatal) (Code 6)	3/2897 (0.001)	0/2306 (0.00)	-----	-----
Self-injurious behavior, no suicidal intent (Code 7)	0/2897 (0.00)	0/2306 (0.00)	-----	-----
Other: accident; psychiatric; medical (Code 8)	188/2897 (0.065)	147/2306 (0.064)	1.02	(0.826, 1.254)
Not enough information (nonfatal) (Code 9)	64/2897 (0.022)	40/2306 (0.017)	1.27	(0.861, 1.883)

n = number of patients having an event

person-years = sum of treatment duration of all patients; duration = (last dose date - first dose date + 1)/365.25

Similar to the results of the FDA requested analysis, our results for short and long-term placebo-controlled trials, show no statistically significant difference of suicidal thinking or behavior in adult sertraline-treated patients versus those treated with placebo.

Conclusion

Due to the above mentioned large sample size of the combination of adult MDD and non-MDD short, and long-term placebo-controlled Zoloft clinical trials, Pfizer believes these data show no statistically significant increased risk of suicidal thinking or behavior in Zoloft treated patients versus those treated with placebo. Accordingly, Pfizer believes that analysis of pooled data across the class of antidepressants should also be informed by medication-specific analysis, where large, well-controlled data are available, as with Zoloft. Pfizer has reviewed these data and finds them to be supportive of Zoloft's safety and effectiveness when used in accordance with the approved package insert.

Sincerely,

Pfizer Inc