Briefing Document

Psychopharmacological Drugs Advisory Committee (PDAC)
and Pediatric Subcommittee of the Anti-Infective Drugs
Advisory Committee (Peds AC)
Advisory Committee

Comments on Behalf of Eli Lilly and Company

13 September 2004

Answers That Matter.

Eli Lilly and Company

Dr. John Hayes
Product Team Leader

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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1. Introduction

Eli Lilly and Company makes this submission in response to the notice of the Food and Drug Administration (FDA) that its Psychopharmacological Drugs Advisory Committee and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee will discuss the results of the Suicidality Classification Project and the analysis of the pediatric suicidality data by the FDA. This meeting is a follow up to a meeting which took place involving these committees on 02 February 2004. Lilly also anticipates, based upon the discussion at that 02 February 2004 meeting that the discussion at the upcoming meeting may also focus on the need for additional research on these topics and data disclosure. Lilly offers the following perspectives on these issues.

Depression is a very serious illness in children and adolescents. Prevalence estimates for major depression in all children range from 16% to 22 % (Costello et al. 1996; Roberts et al. 1998). According to a report from the United States Surgeon General ([HHS] Department of Health and Human Services web page [WWW]), at least "one in ten children and adolescents suffer from mental illness severe enough to cause some level of impairment." Additionally, it states "recent evidence compiled by the World Health Organization indicates that by the year 2020, childhood neuropsychiatric disorders will rise proportionately by over 50 percent, internationally, to become one of the five most common causes of morbidity, mortality, and disability among children." In this same report, it was noted that, in the United States, for children between the ages of 1 and 19 years, the group of conditions that lowers quality of life and reduces life chances (opportunities) the most are emotional and behavioral problems and associated impairments. Children with these disorders are at much increased risk for dropping out of school, and of not being fully functional members of society in adulthood. The cost to society is high in both human and fiscal terms ([HHS] Department of Health and Human Services web page [WWW]). There is also the significant role that stigma plays in inhibiting parents from seeking, and children from receiving, appropriate mental health care. Untreated depression can result in poor social and school performance, family problems, interpersonal difficulties, alienation, isolation, and sometimes, suicide. It is not well appreciated that more teenagers and young adults die from suicide than from cancer, heart disease, AIDS, birth defects, stroke, pneumonia and influenza, and chronic lung disease combined. Suicide is also the fourth leading cause of death among children between the ages of 10 and 14 years (Anderson and Smith 2003). It is important that necessary antidepressant treatments are available to all patients who need them, including children and adolescents. It is additionally important that information regarding the safe use of these products is made publicly available.

At the 02 February 2004 Advisory Committee meeting, the Committee noted that antidepressant label changes should be considered with caution. Lilly would additionally suggest that all classes of antidepressants should be taken into account. Recent label changes have only been implemented for selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). The same label change would also be applicable to other classes of antidepressants. Data have been published showing that the risk of having a suicidal thought or action while taking an antidepressant medication is no greater with any one of the currently available preparations of SSRI, SNRI, or a tricyclic antidepressant (TCA) (Jick et al. 2004).

Following the 02 February 2004 Advisory Committee meeting, the FDA issued class labeling changes on the possibility of worsening of depression and suicidality for all newer SSRIs and SNRIs, including Prozac? (fluoxetine hydrochloride), which is manufactured by Lilly. Lilly fully complied with the requested changes. Recently, the FDA has approved Lilly's Cymbalta? (duloxetine hydrochloride) for use in adults for the treatment for major depressive disorder (MDD). The requested class labeling has also been incorporated in the Cymbalta? package insert. Prozac? is approved for the treatment of major depressive disorder (MDD) and obsessive compulsive disease (OCD) in pediatric population. To date, there are no clinical studies of Cymbalta? in children or adolescents.

2. Brief Review of Fluoxetine Pediatric Data

2.1. General Information

The study reports and the corresponding integrated safety of summary (ISS) for all five trials of Prozac? in children and adolescents were submitted to FDA in September 2000 as a New Drug Application (NDA) for Prozac? in the pediatric indication in major depressive disorder (MDD) and obsessive compulsive disease (OCD).

After reviewing the clinical trial data, the FDA approved Prozac? for the treatment of MDD in children and adolescents on 03 January 2003. Prozac? was the first and continues to be the only antidepressant approved by the FDA for the safe and effective treatment of depression in children and adolescents. Prozac? has also been approved by FDA for use in children and adolescents to treat OCD, a potentially disabling and life-threatening condition.

All five clinical trials of Prozac? in children and adolescents have been published in independent, peer-review journals. Four of the five trials demonstrated the efficacy and safety of Prozac? in children and adolescents. One trial, a pilot study, did not demonstrate the efficacy of Prozac? in children and adolescents. The table below lists the trials and corresponding journal articles.

Eli Lilly Study code	Related Publications
HCCJ	Simeon JG, Dinicola VF, Ferguson HB, Copping W. 1990. Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. Prog Neuropsychopharmacol Biol Psychiatry 14(5):791-795.
HCJE	Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, Nilsson M, Jacobson JG. 2002. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry 41(10):1205-1215.
HCJW	Geller DA, Hoog SL, Heiligenstein JH, Ricardi RK, Tamura R, Kluszynski S, Jacobson JG, and the fluoxetine pediatric OCD study team. 2001. Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. J Am Acad Child Adolesc Psychiatry 40(7):773-779.
X065	Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J. 1997. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arc Gen Psychiatry 54(11):1031-1037. Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Carmody T, Mayes TL. 1998. Fluoxetine in child and adolescent depression: acute and maintenance treatment. Depress Anxiety 7(1):32-39.
HCIU	Wilens TE, Cohen L, Biederman J, Abrams A, Neft D, Faird N, Sinha V. 2002. Fluoxetine pharmacokinetics in pediatric patients. J Clin Psychopharmacol 22(6):568-575.

The table below lists additional manuscripts, from study HCJE, which have been submitted for publication.

Eli Lilly Study code	Submitted Publications
HCJE	Emslie GJ, Heiligenstein JH, Hoog SL, Wagner KD, Findling RL, McCracken JT, Nilsson ME, Jacobson JG. Submitted 2003.Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. J Am Acad Child Adolesc Psychiatry. Nilsson ME, Joliat MJ, Miner CM, Brown EB, Heiligenstein JH. In press 2004. Safety of subchronic treatment with fluoxetine for major depressive disorder in children and adolescents. J Child Adolesc Psychopharmacol.

In addition to these journal publications, multiple poster presentations of the data have been presented at several global conferences, including the 2001 Annual Meeting of the American Academy of Child and Adolescent Psychiatry.

2.2. Suicide-Related Information

Analyses of suicide and self-harm related data were submitted to the FDA on 02 September 2003 and updated on 08 December 2003. Table 1 and Table 2 provide a summary of the analyses. The analyses do not support an association of suicide-related events with fluoxetine treatment compared with placebo treatment in pediatric patients.

Table 1. Risk and Rate of Patients With Suicide-Related Events, "On Therapy"

Population	Indication/Study	Treatment	N	n	%	p-value[a]
All Patients	Depression (overall)	Fluoxetine	178	6	3.4	.786
		Placebo	177	7	4.0	
	HCCJ	Fluoxetine	21	0	0	
		Placebo	19	1	5.3	
	HCJE	Fluoxetine	109	4	3.7	
		Placebo	110	4	3.6	
	X065	Fluoxetine	48	2	4.2	
		Placebo	48	2	4.2	
	OCD (HCJW and overall)	Fluoxetine	71	2	2.8	1.000
		Placebo	32	1	3.1	
	Overall (All indications)	Fluoxetine	249	8	3.2	.801
		Placebo	209	8	3.8	

Abbreviations: N = total number of patients; n = number of patients with event; OCD = obsessive-compulsive disorder.

[a] P-values were determined for each indication and for all indications combined, but not for individual studies; Fisher's exact test.

Table 2. Risk and Rate of Patients With Suicide Attempts, "On Therapy"

Population	Indication/Study	Treatment	N	n	%	p-value[a]
All Patients	Depression (overall)	Fluoxetine	178	3	1.7	1.000
		Placebo	177	3	1.7	
	HCCJ	Fluoxetine	21	0	0	
		Placebo	19	1	5.3	
	HCJE	Fluoxetine	109	1	0.9	
		Placebo	110	2	1.8	
	X065	Fluoxetine	48	2	4.2	
		Placebo	48	0	0	
	OCD (HCJW and overall)	Fluoxetine	71	2	2.8	1.000
		Placebo	32	1	3.1	
	Overall (All indications)	Fluoxetine	249	5	2.0	1.000
		Placebo	209	4	1.9	

Abbreviations: N = total number of patients; n = number of patients with event; OCD = obsessive-compulsive disorder.

[a] P-values were determined for each indication and for all indications combined, but not for individual studies; Fisher's exact test.

The data analysis on suicidality in children, provided to the FDA, was submitted to the 51st Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October 19-24 2004 cited below:

- Martynov O, Acharya N, Joliat M, Nilsson M, Cavazzoni P. Submitted 2004. Analysis of suicidality in children and adolescents treated with fluoxetine. Am Acad Child Adolesc Psychiatry.

3. Summary of Lilly's Policy Regarding Public Disclosure of Medical Research

During the 02 February 2004 Advisory Committee meeting, committee members expressed concern about appropriate disclosure of results from medical research. As noted in Section 2 of this document, data from all 5 fluoxetine clinical trials in children and adolescents have been published and results of the suicide-related outcomes from the 4 placebo-controlled trials have been submitted to the 51st Annual Meeting of the American Academy of Child and Adolescent Psychiatry.

Lilly has had a long-standing commitment to provide our customers with "answers that matter." We strive to provide clear information about all our products and responses to questions that add value to the healthcare decision process.

Existing company policies and industry codes were consolidated and further defined in Lilly's Principles of Medical Research (Attachment 1), which are our standards for conducting, funding and communicating the results of our medical research, whereby we commit to disclosing results significant to patients, healthcare providers, and payers.

Lilly understands that patients, customers, and critics are looking for transparent answers that provide value to the health care decision-making process. Therefore, Lilly has enhanced the pre-existing Principles of Medical Research by committing to disclose publicly the results of all clinical trials on marketed products for which Lilly is a sponsor via a publicly available registry. Consistent with the company's policy of open disclosure, the registry will include the results of all Phase 1 (early exploratory), Phase 2 (proof of concept), Phase 3 (registration), and Phase 4 (post marketing) trials conducted anywhere in the world. See Attachment 2 for a copy of this policy.

For each clinical trial of a marketed product, the company will disclose publicly the results corresponding to the predefined primary and secondary outcome measures specified in the study protocol, as well as relevant additional safety and efficacy results that impact patient care and the clinical use of Lilly products. Results that do not support the hypothesis being tested or that are contrary to the expected outcome will also be disclosed. In addition, Lilly will post a comprehensive description of the trial design and methodology for each study.

Additionally, a listing of all Phase 3 and Phase 4 trials will be posted on the registry at the initiation of each study using a unique study identifier. When the trial is completed and the drug is commercially available, the results of the trial will be appended to its identifier.

For Phase 1, 2, and 3 studies, Lilly will disclose clinical trial results when the indication for the drug is approved and the medication is commercially available. Phase 3 trial results for secondary indications of marketed drugs that fail to achieve approval will also be posted. For Phase 4 studies, Lilly will disclose clinical trial results as soon as possible after the data analysis is completed but no later than one year after the completion of the trial. For studies that are under review by a peer-reviewed journal that prohibits pre-publication disclosure of results, the results will be posted on the registry at the time of the publication.

In all cases, Lilly will disclose clinical trial results on a publicly available, online registry. Lilly also will seek to disclose results through peer-reviewed medical journals, subject to the discretion of the journal editors. The company will commit to providing a reference

in the clinical trial registry for study results that are disclosed in a peer-reviewed journal. In addition, Lilly's clinical trial results may be disclosed through presentations or abstract submissions at professional scientific meetings.

The registry information will be made publicly available beginning in the fourth quarter of this year via www.lillytrials.com. Lilly reaffirms its commitment to continue posting information on the initiation by Lilly of clinical trials for serious and life-threatening diseases via the US government web site, www.clinicaltrials.gov.

4. References

Anderson RN, Smith BL. 2003. Deaths: leading causes for 2001. National vital statistics reports; vol 52 no 9. Hyattsville, Maryland: National Center for Health Statistics. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_09.pdf. Accessed 05 August 2004.

Costello EJ, Angold A, Burns BJ, Stangl DK, Tweed DL, Erkanli A, Worthman CM. 1996. The Great Smoky Mountains study of youth: goals, design, methods, and the prevalence of DSM-III-R disorders. Arch Gen Psychiatry 53(12):1129-1136.

Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J. 1997. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arc Gen Psychiatry 54(11):1031-1037.

Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Carmody T, Mayes TL. 1998. Fluoxetine in child and adolescent depression: acute and maintenance treatment. Depress Anxiety 7(1):32-39.

Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, Nilsson M, Jacobson JG. 2002. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry 41(10):1205-1215.

Emslie GJ, Heiligenstein JH, Hoog SL, Wagner KD, Findling RL, McCracken JT, Nilsson ME, Jacobson JG. Submitted 2003.Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. J Am Acad Child Adolesc Psychiatry.

Geller DA, Hoog SL, Heiligenstein JH, Ricardi RK, Tamura R, Kluszynski S, Jacobson JG, and the fluoxetine pediatric OCD study team. 2001. Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. J Am Acad Child Adolesc Psychiatry 40(7):773-779.

[HHS] Department of Health and Human Services. 2000. U.S. public health service report of the Surgeon General's conference on children's mental health: a national action agenda. Washington, DC: (HHS) Department of Health and Human Services. Available at: http://www.surgeongeneral.gov/topics/cmh/childreport.htm. Accessed 04 August 2004.

Jick H, Kaye JA, Jick SS. 2004. Antidepressants and the risk of suicidal behaviors. JAMA 292(3):338-343.

Martynov O, Acharya N, Joliat M, Nilsson M, Cavazzoni P. Submitted 2004. Analysis of suicidality in children and adolescents treated with fluoxetine. Am Acad Child Adolesc Psychiatry.

Nilsson ME, Joliat MJ, Miner CM, Brown EB, Heiligenstein JH. In press 2004. Safety of subchronic treatment with fluoxetine for major depressive disorder in children and adolescents. J Child Adolesc Psychopharmacol.

Roberts RE, Roberts CR, Chen YR. 1998. Suicidal thinking among adolescents with a history of attempted suicide. J Am Acad Child Adolesc Psychiatry 37(12):1294-1300.

Simeon JG, Dinicola VF, Ferguson HB, Copping W. 1990. Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. Prog Neuropsychopharmacol Biol Psychiatry 14(5):791-795.

Wilens TE, Cohen L, Biederman J, Abrams A, Neft D, Faird N, Sinha V. 2002. Fluoxetine pharmacokinetics in pediatric patients. J Clin Psychopharmacol 22(6):568-575.

Attachment 1.
Principles of Medical Research

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Attachment 2.
Clinical Trial Registry

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