

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 18-936/S-093**

**NDA 21-235/S-016**

***Trade Name:*** Prozac and Prozac Weekly

***Generic Name:*** fluoxetine HCl

***Sponsor:*** Lilly

***Approval Date:*** April 4, 2011

***, QGIFDMRQ*** Revisions to the following section 8.1 of the label.

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*APPLICATION NUMBER:*

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**NDA 18-936/S-093**

**NDA 21-235/S-016**

**APPROVAL LETTER**



NDA 018936/S-091/S-093/S-095  
NDA 021235/S-015/S-016/S-017

## SUPPLEMENT APPROVAL

Eli Lilly & Company  
Attention: Kevin C. Sheehan, MS, Pharm.D.  
Manager, Global Regulatory Affairs - US  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Sheehan:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received May 21, 2009 (018936/S-091 and 021235/S-015), November 6, 2009 (018936/S-093 and 021235/S-016), and April 14, 2010 (018936/S-095 and 021235/S-017), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Prozac (fluoxetine hydrochloride) 10 mg, 20 mg, and 40 mg capsules and Prozac Weekly (fluoxetine hydrochloride) 90 mg delayed-release capsules.

We acknowledge receipt of your amendments dated November 12, 2009, September 13, 2010, October 22, 2010, March 23, 2011, and March 25, 2011.

Your October 22, 2010, submission constituted a complete response to our September 24, 2010, action letter for applications 018936/S-095 and 021235/S-017.

We also refer to your March 22, 2011, email correspondence providing changes to FDA's March 15, 2011 proposed labeling which resulted in mutual labeling agreement.

Please note that this letter corrects our letter dated April 4, 2011, in which text was inadvertently added to the letter. This letter serves as the official document, retaining the approval date of April 4, 2011.

These supplemental applications provide for the following revisions to product labeling:

### **018936/S-091 & 021235/S-015, submitted as "Prior Approval" supplements:**

1. Revisions to Section 6.2 (Other Reactions)
  - Addition of 4 new Medical Dictionary of Regulatory Activities (MedDRA) adverse reaction terms (i.e. Balance Disorder, Bruxism, Gynecological Bleeding, and Hypotension)

- Reinstatement of 3 Adverse Reaction terms (i.e. Alopecia, Dysuria, and Micturition Disorder)
  - Inclusion of the adverse event term depersonalization
2. The following minor additional changes:
- Deletion of “have not been established” at the end of Section 2.6
  - Revisions to Description Data Source in Sections 5.3, 5.4, 5.5, and 6.1
  - Minor editorial changes

**018936/S-093 & 021235/S-016, submitted as “Changes Being Effected” supplements:**

1. Revision to Section 8.1 (Pregnancy) to add a statement to the Pregnancy section of the Prozac (fluoxetine) label that states a potential risk of cardiovascular defects in infants of women who were exposed to fluoxetine during the first trimester of pregnancy.
2. Deletion of label language from Prozac USPI and Medication Guide related to the discontinued Prozac Oral Solution.

**018936/S-095 & 021235/S-017, submitted as “Prior Approval” supplements:**

- These supplements provide for a comprehensive Medication Guide as requested in Agency correspondence dated March 15, 2010.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(I)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to, except with the revisions indicated, the enclosed labeling (text for the package insert and Medication Guide) with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes with the revisions approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact CDR Kofi Ansah, Senior Regulatory Project Manager, at (301)796-4158.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure: Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN  
04/04/2011

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**NDA 18-936/S-093**

**NDA 21-235/S-016**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use PROZAC safely and effectively. See full prescribing information for PROZAC.

PROZAC (fluoxetine hydrochloride) Pulvules for oral use

PROZAC (fluoxetine hydrochloride) delayed-release capsules for oral use

Initial U.S. Approval: 1987

**WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS**

*See full prescribing information for complete boxed warning.*

**Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for Major Depressive Disorder (MDD) and other psychiatric disorders (5.1).**

*When using PROZAC and olanzapine in combination, also refer to Boxed Warning section of the package insert for Symbyax.*

**RECENT MAJOR CHANGES**

**INDICATIONS AND USAGE**

PROZAC® is a selective serotonin reuptake inhibitor indicated for:

- Acute and maintenance treatment of Major Depressive Disorder (MDD) in adult and pediatric patients aged 8 to 18 years (1.1)
- Acute and maintenance treatment of Obsessive Compulsive Disorder (OCD) in adult and pediatric patients aged 7 to 17 years (1.2)
- Acute and maintenance treatment of Bulimia Nervosa in adult patients (1.3)
- Acute treatment of Panic Disorder, with or without agoraphobia, in adult patients (1.4)

PROZAC and olanzapine in combination for:

- Acute treatment of Depressive Episodes Associated with Bipolar I Disorder in adults (1.5)
- Acute treatment of Treatment Resistant Depression in adults (Major Depressive Disorder in adult patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) (1.6)

**DOSAGE AND ADMINISTRATION**

Indication	Adult	Pediatric
MDD (2.1)	20 mg/day in am (initial dose)	10 to 20 mg/day (initial dose)
OCD (2.2)	20 mg/day in am (initial dose)	10 mg/day (initial dose)
Bulimia Nervosa (2.3)	60 mg/day in am	-
Panic Disorder (2.4)	10 mg/day (initial dose)	-
Depressive Episodes Associated with Bipolar I Disorder (2.5)	Oral in combination with olanzapine: 5 mg of oral olanzapine and 20 mg of fluoxetine once daily (initial dose)	-
Treatment Resistant Depression (2.6)	Oral in combination with olanzapine: 5 mg of oral olanzapine and 20 mg of fluoxetine once daily (initial dose)	-

- Consider tapering the dose of fluoxetine for pregnant women during the third trimester (2.7)
- A lower or less frequent dosage should be used in patients with hepatic impairment, the elderly, and for patients with concurrent disease or on multiple concomitant medications (2.7)
- Dosing with PROZAC Weekly capsules - initiate 7 days after the last daily dose of PROZAC 20 mg (2.1)

PROZAC and olanzapine in combination

- Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability (2.5, 2.6)
- Fluoxetine monotherapy is not indicated for the treatment of Depressive Episodes associated with Bipolar I Disorder or treatment resistant depression (2.5, 2.6)

- Safety of the coadministration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated (2.5, 2.6)

**DOSAGE FORMS AND STRENGTHS**

- Pulvules: 10 mg, 20 mg, 40 mg (3)
- Weekly capsules: 90 mg (3)

**CONTRAINDICATIONS**

- Do not use with an MAOI or within 14 days of discontinuing an MAOI due to risk of drug interaction. At least 5 weeks should be allowed after stopping PROZAC before treatment with an MAOI (4, 7.1)
- Do not use with pimozide due to risk of drug interaction or QT<sub>c</sub> prolongation (4, 7.9)
- Do not use with thioridazine due to QT<sub>c</sub> interval prolongation or potential for elevated thioridazine plasma levels. Do not use thioridazine within 5 weeks of discontinuing PROZAC (4, 7.9)
- When using PROZAC and olanzapine in combination, also refer to the Contraindications section of the package insert for Symbyax (4)

**WARNINGS AND PRECAUTIONS**

- *Clinical Worsening and Suicide Risk* Monitor for clinical worsening and suicidal thinking and behavior (5.1)
- *Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions* Have been reported with PROZAC. Discontinue PROZAC and initiate supportive treatment (5.2)
- *Allergic Reactions and Rash* Discontinue upon appearance of rash or allergic phenomena (5.3)
- *Activation of Mania/Hypomania*: Screen for Bipolar Disorder and monitor for mania/hypomania (5.4)
- *Seizures* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold (5.5)
- *Altered Appetite and Weight* Significant weight loss has occurred (5.6)
- *Abnormal Bleeding* May increase the risk of bleeding. Use with NSAIDs, aspirin, warfarin, or drugs that affect coagulation may potentiate the risk of gastrointestinal or other bleeding (5.7)
- *Hyponatremia* Has been reported with PROZAC in association with syndrome of inappropriate antidiuretic hormone (SIADH) (5.8)
- *Anxiety and Insomnia* May occur (5.9)
- *Potential for Cognitive and Motor Impairment* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery (5.11)
- *Long Half-Life* Changes in dose will not be fully reflected in plasma for several weeks (5.12)
- *PROZAC and Olanzapine in Combination* When using PROZAC and olanzapine in combination, also refer to the Warnings and Precautions section of the package insert for Symbyax (5.14)

**ADVERSE REACTIONS**

Most common adverse reactions (≥5% and at least twice that for placebo) associated with:

Major Depressive Disorder, Obsessive Compulsive Disorder, Bulimia, and Panic Disorder: abnormal dreams, abnormal ejaculation, anorexia, anxiety, asthenia, diarrhea, dry mouth, dyspepsia, flu syndrome, impotence, insomnia, libido decreased, nausea, nervousness, pharyngitis, rash, sinusitis, somnolence, sweating, tremor, vasodilatation, and yawn (6.1)

PROZAC and olanzapine in combination – Also refer to the Adverse Reactions section of the package insert for Symbyax (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

**DRUG INTERACTIONS**

- *Monoamine Oxidase Inhibitors (MAOI)* PROZAC is contraindicated for use with MAOI's, or within 14 days of discontinuing an MAOI due to risk of drug interaction. At least 5 weeks should be allowed after stopping PROZAC before starting treatment with an MAOI (4, 7.1)
- *Pimozide* PROZAC is contraindicated for use with pimozide due to risk of drug interaction or QT<sub>c</sub> prolongation (4, 7.9)
- *Thioridazine* PROZAC is contraindicated for use with thioridazine due to QT<sub>c</sub> interval prolongation or potential for elevated thioridazine plasma levels. Do not use thioridazine within 5 weeks of discontinuing PROZAC (4, 7.9)
- *Drugs Metabolized by CYP2D6*: Fluoxetine is a potent inhibitor of CYP2D6 enzyme pathway (7.9)

- *Tricyclic Antidepressants (TCAs)* Monitor TCA levels during coadministration with PROZAC or when PROZAC has been recently discontinued (7.9)
- *CNS Acting Drugs* Caution should be used when taken in combination with other centrally acting drugs (7.2)
- *Benzodiazepines* Diazepam – increased t<sub>1/2</sub>, alprazolam - further psychomotor performance decrement due to increased levels (7.9)
- *Antipsychotics* Potential for elevation of haloperidol and clozapine levels (7.9)
- *Anticonvulsants* Potential for elevated phenytoin and carbamazepine levels and clinical anticonvulsant toxicity (7.9)
- *Serotonergic Drugs* Potential for Serotonin Syndrome (5.2, 7.3)
- *Triptans* There have been rare postmarketing reports of Serotonin Syndrome with use of an SSRI and a triptan (5.2, 7.4)
- *Tryptophan* Concomitant use with tryptophan is not recommended (5.2, 7.5)
- *Drugs that Interfere with Hemostasis (e.g. NSAIDs, Aspirin, Warfarin)* May potentiate the risk of bleeding (7.6)

- *Drugs Tightly Bound to Plasma Proteins:* May cause a shift in plasma concentrations (7.8, 7.9)
- *Olanzapine:* When used in combination with PROZAC, also refer to the Drug Interactions section of the package insert for Symbyax (7.9)

#### -----USE IN SPECIFIC POPULATIONS-----

- *Pregnancy* PROZAC should be used during pregnancy only if the potential benefit justifies the potential risks to the fetus (8.1)
- *Nursing Mothers* Breast feeding is not recommended (8.3)
- *Pediatric Use:* Safety and effectiveness of PROZAC and olanzapine in combination have not been established in patients less than 18 years of age (8.4)
- *Hepatic Impairment* Lower or less frequent dosing may be appropriate in patients with cirrhosis (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: [00/0000]

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\*Sections or subsections omitted from the full prescribing information are not listed

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**FULL PRESCRIBING INFORMATION**
**WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS**

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PROZAC or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PROZAC is approved for use in pediatric patients with MDD and Obsessive Compulsive Disorder (OCD) [see Warnings and Precautions (5.1) and Use in Specific Populations (8.4)].

When using PROZAC and olanzapine in combination, also refer to Boxed Warning section of the package insert for Symbyax.

**1 INDICATIONS AND USAGE**
**1.1 Major Depressive Disorder**

PROZAC<sup>®</sup> is indicated for the acute and maintenance treatment of Major Depressive Disorder in adult patients and in pediatric patients aged 8 to 18 years [see Clinical Studies (14.1)].

The usefulness of the drug in adult and pediatric patients receiving fluoxetine for extended periods, should periodically be re-evaluated [see Dosage and Administration (2.1)].

**1.2 Obsessive Compulsive Disorder**

PROZAC is indicated for the acute and maintenance treatment of obsessions and compulsions in adult patients and in pediatric patients aged 7 to 17 years with Obsessive Compulsive Disorder (OCD) [see Clinical Studies (14.2)].

The effectiveness of PROZAC in long-term use, i.e., for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use PROZAC for extended periods, should periodically re-evaluate the long-term usefulness of the drug for the individual patient [see Dosage and Administration (2.2)].

**1.3 Bulimia Nervosa**

PROZAC is indicated for the acute and maintenance treatment of binge-eating and vomiting behaviors in adult patients with moderate to severe Bulimia Nervosa [see Clinical Studies (14.3)].

The physician who elects to use PROZAC for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient [see Dosage and Administration (2.3)].

**1.4 Panic Disorder**

PROZAC is indicated for the acute treatment of Panic Disorder, with or without agoraphobia, in adult patients [see Clinical Studies (14.4)].

The effectiveness of PROZAC in long-term use, i.e., for more than 12 weeks, has not been established in placebo-controlled trials. Therefore, the physician who elects to use PROZAC for extended periods, should periodically re-evaluate the long-term usefulness of the drug for the individual patient [see Dosage and Administration (2.4)].

**1.5 PROZAC and Olanzapine in Combination: Depressive Episodes Associated with Bipolar I Disorder**

When using PROZAC and olanzapine in combination, also refer to the Clinical Studies section of the package insert for Symbyax<sup>®</sup>.

PROZAC and olanzapine in combination is indicated for the acute treatment of depressive episodes associated with Bipolar I Disorder in adult patients.

PROZAC monotherapy is not indicated for the treatment of depressive episodes associated with Bipolar I Disorder.

**1.6 PROZAC and Olanzapine in Combination: Treatment Resistant Depression**

When using PROZAC and olanzapine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

PROZAC and olanzapine in combination is indicated for the acute treatment of treatment resistant depression (Major Depressive Disorder in adult patients, who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode).

PROZAC monotherapy is not indicated for the treatment of treatment resistant depression.

**2 DOSAGE AND ADMINISTRATION**
**2.1 Major Depressive Disorder**

*Initial Treatment*

*Adult* — In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 to 80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response in Major Depressive Disorder in most cases. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

*Pediatric (children and adolescents)* — In the short-term (8 to 9 week) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of Major Depressive Disorder, patients were administered fluoxetine doses of 10 to 20 mg/day [see *Clinical Studies (14.1)*]. Treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day.

However, due to higher plasma levels in lower weight children, the starting and target dose in this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several weeks if insufficient clinical improvement is observed.

*All patients* — As with other drugs effective in the treatment of Major Depressive Disorder, the full effect may be delayed until 4 weeks of treatment or longer.

*Maintenance/Continuation/Extended Treatment* — It is generally agreed that acute episodes of Major Depressive Disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

*Daily Dosing* — Systematic evaluation of PROZAC in adult patients has shown that its efficacy in Major Depressive Disorder is maintained for periods of up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) at a dose of 20 mg/day [see *Clinical Studies (14.1)*].

*Weekly Dosing* — Systematic evaluation of PROZAC<sup>®</sup> Weekly<sup>™</sup> in adult patients has shown that its efficacy in Major Depressive Disorder is maintained for periods of up to 25 weeks with once-weekly dosing following 13 weeks of open-label treatment with PROZAC 20 mg once daily. However, therapeutic equivalence of PROZAC Weekly given on a once-weekly basis with PROZAC 20 mg given daily for delaying time to relapse has not been established [see *Clinical Studies (14.1)*].

Weekly dosing with PROZAC Weekly capsules is recommended to be initiated 7 days after the last daily dose of PROZAC 20 mg [see *Clinical Pharmacology (12.3)*].

If satisfactory response is not maintained with PROZAC Weekly, consider reestablishing a daily dosing regimen [see *Clinical Studies (14.1)*].

*Switching Patients to a Tricyclic Antidepressant (TCA)* — Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued [see *Drug Interactions (7.9)*].

*Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI)* — At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with PROZAC. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping PROZAC before starting an MAOI [see *Contraindications (4) and Drug Interactions (7.1)*].

## 2.2 Obsessive Compulsive Disorder

### *Initial Treatment*

*Adult* — In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo [see *Clinical Studies (14.2)*]. In one of these studies, no dose-response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose-response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once daily (i.e., morning) or BID schedule (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended; however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

*Pediatric (children and adolescents)* — In the controlled clinical trial of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the range of 10 to 60 mg/day [see *Clinical Studies (14.2)*].

In adolescents and higher weight children, treatment should be initiated with a dose of 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 60 mg/day is recommended.

In lower weight children, treatment should be initiated with a dose of 10 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 30 mg/day is recommended. Experience with daily doses greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg.

*Maintenance/Continuation Treatment* — While there are no systematic studies that answer the question of how long to continue PROZAC, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of PROZAC after 13 weeks has not been documented in controlled trials, adult patients have been continued in therapy under

double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

### 2.3 Bulimia Nervosa

*Initial Treatment* — In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of Bulimia Nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or placebo [see *Clinical Studies (14.3)*]. Only the 60 mg dose was statistically significantly superior to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the recommended dose is 60 mg/day, administered in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with bulimia.

*Maintenance/Continuation Treatment* — Systematic evaluation of continuing PROZAC 60 mg/day for periods of up to 52 weeks in patients with bulimia who have responded while taking PROZAC 60 mg/day during an 8-week acute treatment phase has demonstrated a benefit of such maintenance treatment [see *Clinical Studies (14.3)*]. Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

### 2.4 Panic Disorder

*Initial Treatment* — In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of Panic Disorder, patients were administered fluoxetine doses in the range of 10 to 60 mg/day [see *Clinical Studies (14.4)*]. Treatment should be initiated with a dose of 10 mg/day. After one week, the dose should be increased to 20 mg/day. The most frequently administered dose in the 2 flexible-dose clinical trials was 20 mg/day.

A dose increase may be considered after several weeks if no clinical improvement is observed. Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with Panic Disorder.

*Maintenance/Continuation Treatment* — While there are no systematic studies that answer the question of how long to continue PROZAC, panic disorder is a chronic condition and it is reasonable to consider continuation for a responding patient. Nevertheless, patients should be periodically reassessed to determine the need for continued treatment.

### 2.5 PROZAC and Olanzapine in Combination: Depressive Episodes Associated with Bipolar I Disorder

*When using PROZAC and olanzapine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.*

Fluoxetine should be administered in combination with oral olanzapine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of fluoxetine 20 to 50 mg and oral olanzapine 5 to 12.5 mg. Antidepressant efficacy was demonstrated with olanzapine and fluoxetine in combination with a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of fluoxetine in combination with olanzapine was determined in clinical trials supporting approval of Symbyax (fixed-dose combination of olanzapine and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. The following table demonstrates the appropriate individual component doses of PROZAC and olanzapine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

**Table 1: Approximate Dose Correspondence Between Symbyax<sup>1</sup> and the Combination of PROZAC and Olanzapine**

For Symbyax (mg/day)	Use in Combination	
	Olanzapine (mg/day)	PROZAC (mg/day)
3 mg olanzapine/25 mg fluoxetine	2.5	20
6 mg olanzapine/25 mg fluoxetine	5	20
12 mg olanzapine/25 mg fluoxetine	10+2.5	20
6 mg olanzapine/50 mg fluoxetine	5	40+10
12 mg olanzapine/50 mg fluoxetine	10+2.5	40+10

<sup>1</sup> Symbyax (olanzapine/fluoxetine HCL) is a fixed-dose combination of PROZAC and olanzapine.

While there is no body of evidence to answer the question of how long a patient treated with PROZAC and olanzapine in combination should remain on it, it is generally accepted that Bipolar I Disorder, including the depressive episodes associated with Bipolar I Disorder, is a chronic illness requiring chronic treatment. The physician should periodically re-examine the need for continued pharmacotherapy.

Safety of coadministration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies. PROZAC monotherapy is not indicated for the treatment of depressive episodes associated with Bipolar I Disorder.

### 2.6 PROZAC and Olanzapine in Combination: Treatment Resistant Depression

*When using PROZAC and olanzapine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.*

Fluoxetine should be administered in combination with oral olanzapine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to

efficacy and tolerability within dose ranges of fluoxetine 20 to 50 mg and oral olanzapine 5 to 20 mg. Antidepressant efficacy was demonstrated with olanzapine and fluoxetine in combination with a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of fluoxetine in combination with olanzapine was determined in clinical trials supporting approval of Symbyax (fixed dose combination of olanzapine and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. Table 1 demonstrates the appropriate individual component doses of PROZAC and olanzapine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

While there is no body of evidence to answer the question of how long a patient treated with PROZAC and olanzapine in combination should remain on it, it is generally accepted that treatment resistant depression (Major Depressive Disorder in adult patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) is a chronic illness requiring chronic treatment. The physician should periodically re-examine the need for continued pharmacotherapy.

Safety of coadministration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

PROZAC monotherapy is not indicated for the treatment of treatment resistant depression (Major Depressive Disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode).

## 2.7 Dosing in Specific Populations

*Treatment of Pregnant Women during the Third Trimester* — When treating pregnant women with PROZAC during the third trimester, the physician should carefully consider the potential risks and potential benefits of treatment. Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. The physician may consider tapering PROZAC in the third trimester [see *Use in Specific Populations* (8.1)].

*Geriatric* — A lower or less frequent dosage should be considered for the elderly [see *Use in Specific Populations* (8.5)].

*Hepatic Impairment* — As with many other medications, a lower or less frequent dosage should be used in patients with hepatic impairment [see *Clinical Pharmacology* (12.4) and *Use in Specific Populations* (8.6)].

*Concomitant Illness* — Patients with concurrent disease or on multiple concomitant medications may require dosage adjustments [see *Clinical Pharmacology* (12.4) and *Warnings and Precautions* (5.10)].

*PROZAC and Olanzapine in Combination* — The starting dose of oral olanzapine 2.5 to 5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, non-smoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modifications may be necessary in patients who exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients. PROZAC and olanzapine in combination have not been systematically studied in patients over 65 years of age or in patients less than 18 years of age [see *Warnings and Precautions* (5.14) and *Drug Interactions* (7.9)].

## 2.8 Discontinuation of Treatment

Symptoms associated with discontinuation of fluoxetine, SNRIs, and SSRIs, have been reported [see *Warnings and Precautions* (5.13)].

## 3 DOSAGE FORMS AND STRENGTHS

- 10 mg Pulvule is an opaque green cap and opaque green body, imprinted with DISTA 3104 on the cap and Prozac 10 mg on the body
- 20 mg Pulvule is an opaque green cap and opaque yellow body, imprinted with DISTA 3105 on the cap and Prozac 20 mg on the body
- 40 mg Pulvule is an opaque green cap and opaque orange body, imprinted with DISTA 3107 on the cap and Prozac 40 mg on the body
- 90 mg Prozac Weekly™ Capsule is an opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with Lilly on the cap and 3004 and 90 mg on the body

## 4 CONTRAINDICATIONS

When using PROZAC and olanzapine in combination, also refer to the *Contraindications* section of the package insert for Symbyax.

The use of PROZAC is contraindicated with the following:

- Monoamine Oxidase Inhibitors [see *Drug Interactions* (7.1)]
- Pimozide [see *Drug Interactions* (7.9)]
- Thioridazine [see *Drug Interactions* (7.9)]

## 5 WARNINGS AND PRECAUTIONS

When using PROZAC and olanzapine in combination, also refer to the *Warnings and Precautions* section of the package insert for Symbyax.

### 5.1 Clinical Worsening and Suicide Risk

Patients with Major Depressive Disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking

antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with Major Depressive Disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug versus placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 2.

**Table 2: Suicidality per 1000 Patients Treated**

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

**All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.**

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for Major Depressive Disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [see *Warnings and Precautions (5.13)*].

**Families and caregivers of patients being treated with antidepressants for Major Depressive Disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for PROZAC should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

It should be noted that PROZAC is approved in the pediatric population only for Major Depressive Disorder and Obsessive Compulsive Disorder. Safety and effectiveness of PROZAC and olanzapine in combination in patients less than 18 years of age have not been established.

## **5.2 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions**

The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including PROZAC treatment, but particularly with concomitant use of

serotonergic drugs (including triptans), with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of PROZAC with MAOIs intended to treat depression is contraindicated [*see Contraindications (4) and Drug Interactions (7.1)*].

If concomitant treatment of PROZAC with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Drug Interactions (7.4)*].

The concomitant use of PROZAC with serotonin precursors (such as tryptophan) is not recommended [*see Drug Interactions (7.3)*].

Treatment with fluoxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated.

### 5.3 Allergic Reactions and Rash

In US fluoxetine clinical trials, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these reactions were reported to recover completely.

In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of PROZAC, systemic reactions, possibly related to vasculitis and including lupus-like syndrome, have developed in patients with rash. Although these reactions are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic reactions.

Anaphylactoid reactions, including bronchospasm, angioedema, laryngospasm, and urticaria alone and in combination, have been reported.

Pulmonary reactions, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These reactions have occurred with dyspnea as the only preceding symptom.

Whether these systemic reactions and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these reactions has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, PROZAC should be discontinued.

### 5.4 Screening Patients for Bipolar Disorder and Monitoring for Mania/Hypomania

A major depressive episode may be the initial presentation of Bipolar Disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for Bipolar Disorder. Whether any of the symptoms described for clinical worsening and suicide risk represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for Bipolar Disorder; such screening should include a detailed psychiatric history, including a family history of suicide, Bipolar Disorder, and depression. It should be noted that PROZAC and olanzapine in combination is approved for the acute treatment of depressive episodes associated with Bipolar I Disorder [*see Warnings and Precautions section of the package insert for Symbyax*]. PROZAC monotherapy is not indicated for the treatment of depressive episodes associated with Bipolar I Disorder.

In US placebo-controlled clinical trials for Major Depressive Disorder, mania/hypomania was reported in 0.1% of patients treated with PROZAC and 0.1% of patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed drugs effective in the treatment of Major Depressive Disorder [*see Use in Specific Populations (8.4)*].

In US placebo-controlled clinical trials for OCD, mania/hypomania was reported in 0.8% of patients treated with PROZAC and no patients treated with placebo. No patients reported mania/hypomania in US placebo-controlled clinical trials for bulimia. In US PROZAC clinical trials, 0.7% of 10,782 patients reported mania/hypomania [*see Use in Specific Populations (8.4)*].

### 5.5 Seizures

In US placebo-controlled clinical trials for Major Depressive Disorder, convulsions (or reactions described as possibly having been seizures) were reported in 0.1% of patients treated with PROZAC and 0.2% of patients treated with placebo. No patients reported convulsions in US placebo-controlled clinical trials for either OCD or bulimia. In US PROZAC clinical trials, 0.2% of 10,782 patients

reported convulsions. The percentage appears to be similar to that associated with other marketed drugs effective in the treatment of Major Depressive Disorder. PROZAC should be introduced with care in patients with a history of seizures.

### 5.6 Altered Appetite and Weight

Significant weight loss, especially in underweight depressed or bulimic patients, may be an undesirable result of treatment with PROZAC.

In US placebo-controlled clinical trials for Major Depressive Disorder, 11% of patients treated with PROZAC and 2% of patients treated with placebo reported anorexia (decreased appetite). Weight loss was reported in 1.4% of patients treated with PROZAC and in 0.5% of patients treated with placebo. However, only rarely have patients discontinued treatment with PROZAC because of anorexia or weight loss [see *Use in Specific Populations (8.4)*].

In US placebo-controlled clinical trials for OCD, 17% of patients treated with PROZAC and 10% of patients treated with placebo reported anorexia (decreased appetite). One patient discontinued treatment with PROZAC because of anorexia [see *Use in Specific Populations (8.4)*].

In US placebo-controlled clinical trials for Bulimia Nervosa, 8% of patients treated with PROZAC 60 mg and 4% of patients treated with placebo reported anorexia (decreased appetite). Patients treated with PROZAC 60 mg on average lost 0.45 kg compared with a gain of 0.16 kg by patients treated with placebo in the 16-week double-blind trial. Weight change should be monitored during therapy.

### 5.7 Abnormal Bleeding

SNRIs and SSRIs, including fluoxetine, may increase the risk of bleeding reactions. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding reactions related to SNRIs and SSRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of fluoxetine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation [see *Drug Interactions (7.6)*].

### 5.8 Hyponatremia

Hyponatremia has been reported during treatment with SNRIs and SSRIs, including PROZAC. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when PROZAC was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SNRIs and SSRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [see *Use in Specific Populations (8.5)*]. Discontinuation of PROZAC should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

### 5.9 Anxiety and Insomnia

In US placebo-controlled clinical trials for Major Depressive Disorder, 12% to 16% of patients treated with PROZAC and 7% to 9% of patients treated with placebo reported anxiety, nervousness, or insomnia.

In US placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients treated with PROZAC and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with PROZAC and in 7% of patients treated with placebo.

In US placebo-controlled clinical trials for Bulimia Nervosa, insomnia was reported in 33% of patients treated with PROZAC 60 mg, and 13% of patients treated with placebo. Anxiety and nervousness were reported, respectively, in 15% and 11% of patients treated with PROZAC 60 mg and in 9% and 5% of patients treated with placebo.

Among the most common adverse reactions associated with discontinuation (incidence at least twice that for placebo and at least 1% for PROZAC in clinical trials collecting only a primary reaction associated with discontinuation) in US placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia (1% in combined indications and 2% in bulimia), and nervousness (1% in Major Depressive Disorder) [see *Table 5*].

### 5.10 Use in Patients with Concomitant Illness

Clinical experience with PROZAC in patients with concomitant systemic illness is limited. Caution is advisable in using PROZAC in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

**Cardiovascular** — Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received PROZAC in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

**Glycemic Control** — In patients with diabetes, PROZAC may alter glycemic control. Hypoglycemia has occurred during therapy with PROZAC, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of

medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic, dosage may need to be adjusted when therapy with PROZAC is instituted or discontinued.

#### **5.11 Potential for Cognitive and Motor Impairment**

As with any CNS-active drug, PROZAC has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

#### **5.12 Long Elimination Half-Life**

Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine [*see Clinical Pharmacology (12.3)*].

#### **5.13 Discontinuation of Treatment**

During marketing of PROZAC, SNRIs, and SSRIs, there have been spontaneous reports of adverse reactions occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these reactions are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with PROZAC. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy which may minimize the risk of discontinuation symptoms with this drug.

#### **5.14 PROZAC and Olanzapine in Combination**

When using PROZAC and olanzapine in combination, also refer to the Warnings and Precautions section of the package insert for Symbyax.

### **6 ADVERSE REACTIONS**

*When using PROZAC and olanzapine in combination, also refer to the Adverse Reactions section of the package insert for Symbyax.*

#### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect or predict the rates observed in practice.

Multiple doses of PROZAC have been administered to 10,782 patients with various diagnoses in US clinical trials. In addition, there have been 425 patients administered PROZAC in panic clinical trials. Adverse reactions were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a limited (i.e., reduced) number of standardized reaction categories.

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse reactions. The stated frequencies represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that reactions reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

*Incidence in Major Depressive Disorder, OCD, bulimia, and Panic Disorder placebo-controlled clinical trials (excluding data from extensions of trials)* — Table 3 enumerates the most common treatment-emergent adverse reactions associated with the use of PROZAC (incidence of at least 5% for PROZAC and at least twice that for placebo within at least 1 of the indications) for the treatment of Major Depressive Disorder, OCD, and bulimia in US controlled clinical trials and Panic Disorder in US plus non-US controlled trials. Table 5 enumerates treatment-emergent adverse reactions that occurred in 2% or more patients treated with PROZAC and with incidence greater than placebo who participated in US Major Depressive Disorder, OCD, and bulimia controlled clinical trials and US plus non-US Panic Disorder controlled clinical trials. Table 4 provides combined data for the pool of studies that are provided separately by indication in Table 3.

**Table 3: Most Common Treatment-Emergent Adverse Reactions: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials<sup>1,2</sup>**

Body System/ Adverse Reaction	Percentage of Patients Reporting Event							
	Major Depressive Disorder		OCD		Bulimia		Panic Disorder	
	PROZAC (N=1728)	Placebo (N=975)	PROZAC (N=266)	Placebo (N=89)	PROZAC (N=450)	Placebo (N=267)	PROZAC (N=425)	Placebo (N=342)
<b>Body as a Whole</b>								
Asthenia	9	5	15	11	21	9	7	7
Flu syndrome	3	4	10	7	8	3	5	5
<b>Cardiovascular System</b>								
Vasodilatation	3	2	5	--	2	1	1	--
<b>Digestive System</b>								
Nausea	21	9	26	13	29	11	12	7
Diarrhea	12	8	18	13	8	6	9	4
Anorexia	11	2	17	10	8	4	4	1
Dry mouth	10	7	12	3	9	6	4	4
Dyspepsia	7	5	10	4	10	6	6	2
<b>Nervous System</b>								
Insomnia	16	9	28	22	33	13	10	7
Anxiety	12	7	14	7	15	9	6	2
Nervousness	14	9	14	15	11	5	8	6
Somnolence	13	6	17	7	13	5	5	2
Tremor	10	3	9	1	13	1	3	1
Libido decreased	3	--	11	2	5	1	1	2
Abnormal dreams	1	1	5	2	5	3	1	1
<b>Respiratory System</b>								
Pharyngitis	3	3	11	9	10	5	3	3
Sinusitis	1	4	5	2	6	4	2	3
Yawn	--	--	7	--	11	--	1	--
<b>Skin and Appendages</b>								
Sweating	8	3	7	--	8	3	2	2
Rash	4	3	6	3	4	4	2	2
<b>Urogenital System</b>								
Impotence <sup>3</sup>	2	--	--	--	7	--	1	--
Abnormal ejaculation <sup>3</sup>	--	--	7	--	7	--	2	1

<sup>1</sup> Incidence less than 1%.

<sup>2</sup> Includes US data for Major Depressive Disorder, OCD, Bulimia, and Panic Disorder clinical trials, plus non-US data for Panic Disorder clinical trials.

<sup>3</sup> Denominator used was for males only (N=690 PROZAC Major Depressive Disorder; N=410 placebo Major Depressive Disorder; N=116 PROZAC OCD; N=43 placebo OCD; N=14 PROZAC bulimia; N=1 placebo bulimia; N=162 PROZAC panic; N=121 placebo panic).

**Table 4: Treatment-Emergent Adverse Reactions: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials<sup>1,2</sup>**

	Percentage of Patients Reporting Event
	Major Depressive Disorder, OCD, Bulimia,

<b>Body System/ Adverse Reaction</b>	<b>and Panic Disorder Combined</b>	
	<b>PROZAC (N=2869)</b>	<b>Placebo (N=1673)</b>
<b>Body as a Whole</b>		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
<b>Cardiovascular System</b>		
Vasodilatation	2	1
<b>Digestive System</b>		
Nausea	22	9
Diarrhea	11	7
Anorexia	10	3
Dry mouth	9	6
Dyspepsia	8	4
Constipation	5	4
Flatulence	3	2
Vomiting	3	2
<b>Metabolic and Nutritional Disorders</b>		
Weight loss	2	1
<b>Nervous System</b>		
Insomnia	19	10
Nervousness	13	8
Anxiety	12	6
Somnolence	12	5
Dizziness	9	6
Tremor	9	2
Libido decreased	4	1
Thinking abnormal	2	1
<b>Respiratory System</b>		
Yawn	3	--
<b>Skin and Appendages</b>		
Sweating	7	3
Rash	4	3
Pruritus	3	2
<b>Special Senses</b>		
Abnormal vision	2	1

<sup>1</sup> Incidence less than 1%.

<sup>2</sup> Includes US data for Major Depressive Disorder, OCD, bulimia, and Panic Disorder clinical trials, plus non-US data for Panic Disorder clinical trials.

*Associated with discontinuation in Major Depressive Disorder, OCD, bulimia, and Panic Disorder placebo-controlled clinical trials (excluding data from extensions of trials) — Table 5 lists the adverse reactions associated with discontinuation of PROZAC treatment (incidence at least twice that for placebo and at least 1% for PROZAC in clinical trials collecting only a primary reaction associated with discontinuation) in Major Depressive Disorder, OCD, bulimia, and Panic Disorder clinical trials, plus non-US Panic Disorder clinical trials.*

**Table 5: Most Common Adverse Reactions Associated with Discontinuation in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials<sup>1</sup>**

<b>Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined (N=1533)</b>	<b>Major Depressive Disorder (N=392)</b>	<b>OCD (N=266)</b>	<b>Bulimia (N=450)</b>	<b>Panic Disorder (N=425)</b>

Anxiety (1%)	--	Anxiety (2%)	--	Anxiety (2%)
--	--	--	Insomnia (2%)	--
--	Nervousness (1%)	--	--	Nervousness (1%)
--	--	Rash (1%)	--	--

<sup>1</sup> Includes US Major Depressive Disorder, OCD, bulimia, and Panic Disorder clinical trials, plus non-US Panic Disorder clinical trials.

*Other adverse reactions in pediatric patients (children and adolescents)* — Treatment-emergent adverse reactions were collected in 322 pediatric patients (180 fluoxetine-treated, 142 placebo-treated). The overall profile of adverse reactions was generally similar to that seen in adult studies, as shown in Tables 4 and 5. However, the following adverse reactions (excluding those which appear in the body or footnotes of Tables 4 and 5 and those for which the COSTART terms were uninformative or misleading) were reported at an incidence of at least 2% for fluoxetine and greater than placebo: thirst, hyperkinesia, agitation, personality disorder, epistaxis, urinary frequency, and menorrhagia.

The most common adverse reaction (incidence at least 1% for fluoxetine and greater than placebo) associated with discontinuation in 3 pediatric placebo-controlled trials (N=418 randomized; 228 fluoxetine-treated; 190 placebo-treated) was mania/hypomania (1.8% for fluoxetine-treated, 0% for placebo-treated). In these clinical trials, only a primary reaction associated with discontinuation was collected.

*Reactions observed in PROZAC Weekly clinical trials* — Treatment-emergent adverse reactions in clinical trials with PROZAC Weekly were similar to the adverse reactions reported by patients in clinical trials with PROZAC daily. In a placebo-controlled clinical trial, more patients taking PROZAC Weekly reported diarrhea than patients taking placebo (10% versus 3%, respectively) or taking PROZAC 20 mg daily (10% versus 5%, respectively).

*Male and female sexual dysfunction with SSRIs* — Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance, cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in US Major Depressive Disorder, OCD, and bulimia placebo-controlled clinical trials, decreased libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4% fluoxetine, <1% placebo). There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction, including anorgasmia.

There are no adequate and well-controlled studies examining sexual dysfunction with fluoxetine treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

## 6.2 Other Reactions

Following is a list of treatment-emergent adverse reactions reported by patients treated with fluoxetine in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

**Body as a Whole** — *Frequent*: chills; *Infrequent*: suicide attempt; *Rare*: acute abdominal syndrome, photosensitivity reaction.

**Cardiovascular System** — *Frequent*: palpitation; *Infrequent*: arrhythmia, hypotension<sup>1</sup>.

**Digestive System** — *Infrequent*: dysphagia, gastritis, gastroenteritis, melena, stomach ulcer; *Rare*: bloody diarrhea, duodenal ulcer, esophageal ulcer, gastrointestinal hemorrhage, hematemesis, hepatitis, peptic ulcer, stomach ulcer hemorrhage.

**Hemic and Lymphatic System** — *Infrequent*: ecchymosis; *Rare*: petechia, purpura.

**Nervous System** — *Frequent*: emotional lability; *Infrequent*: akathisia, ataxia, balance disorder<sup>1</sup>, bruxism<sup>1</sup>, buccoglossal syndrome, depersonalization, euphoria, hypertonia, libido increased, myoclonus, paranoid reaction; *Rare*: delusions.

**Respiratory System** — *Rare*: larynx edema.

**Skin and Appendages** — *Infrequent*: alopecia; *Rare*: purpuric rash.

**Special Senses** — *Frequent*: taste perversion; *Infrequent*: mydriasis.

**Urogenital System** — *Frequent*: micturition disorder; *Infrequent*: dysuria, gynecological bleeding<sup>2</sup>.

<sup>1</sup> MedDRA dictionary term from integrated database of placebo controlled trials of 15870 patients, of which 9673 patients received fluoxetine.

- <sup>2</sup> Group term that includes individual MedDRA terms: cervix hemorrhage uterine, dysfunctional uterine bleeding, genital hemorrhage, menometrorrhagia, menorrhagia, metrorrhagia, polymenorrhea, postmenopausal hemorrhage, uterine hemorrhage, vaginal hemorrhage. Adjusted for gender.

### 6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of PROZAC. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Voluntary reports of adverse reactions temporally associated with PROZAC that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation<sup>1</sup>, cataract, cerebrovascular accident<sup>1</sup>, cholestatic jaundice, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia<sup>1</sup>, epidermal necrolysis, erythema multiforme, erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest<sup>1</sup>, hepatic failure/necrosis, hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure, movement disorders developing in patients with risk factors including drugs associated with such reactions and worsening of pre-existing movement disorders, optic neuritis, pancreatitis<sup>1</sup>, pancytopenia, pulmonary embolism, pulmonary hypertension, QT prolongation, Stevens-Johnson syndrome, thrombocytopenia<sup>1</sup>, thrombocytopenic purpura, ventricular tachycardia (including torsades de pointes–type arrhythmias), vaginal bleeding, and violent behaviors<sup>1</sup>.

<sup>1</sup> These terms represent serious adverse events, but do not meet the definition for adverse drug reactions. They are included here because of their seriousness.

## 7 DRUG INTERACTIONS

As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility.

### 7.1 Monoamine Oxidase Inhibitors (MAOI)

There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, PROZAC should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI [*see Contraindications (4)*]. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should be allowed after stopping PROZAC before starting an MAOI [*see Clinical Pharmacology (12.3)*].

### 7.2 CNS Acting Drugs

Caution is advised if the concomitant administration of PROZAC and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status [*see Clinical Pharmacology (12.3)*].

### 7.3 Serotonergic Drugs

Based on the mechanism of action of SNRIs and SSRIs, including PROZAC, and the potential for serotonin syndrome, caution is advised when PROZAC is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort [*see Warnings and Precautions (5.2)*]. The concomitant use of PROZAC with SNRIs, SSRIs, or tryptophan is not recommended [*see Drug Interactions (7.4), (7.5)*].

### 7.4 Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of PROZAC with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Warnings and Precautions (5.2) and Drug Interactions (7.3)*].

### 7.5 Tryptophan

Five patients receiving PROZAC in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress. The concomitant use with tryptophan is not recommended [*see Warnings and Precautions (5.2) and Drug Interactions (7.3)*].

### 7.6 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SNRIs or SSRIs are coadministered

with warfarin. Patients receiving warfarin therapy should be carefully monitored when fluoxetine is initiated or discontinued [*see Warnings and Precautions (5.7)*].

### 7.7 Electroconvulsive Therapy (ECT)

There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

### 7.8 Potential for Other Drugs to affect PROZAC

*Drugs Tightly Bound to Plasma Proteins* — Because fluoxetine is tightly bound to plasma proteins, adverse effects may result from displacement of protein-bound fluoxetine by other tightly-bound drugs [*see Clinical Pharmacology (12.3)*].

### 7.9 Potential for PROZAC to affect Other Drugs

*Pimozide* — Concomitant use in patients taking pimozide is contraindicated. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QT<sub>c</sub> prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT<sub>c</sub> prolongation warrants restricting the concurrent use of pimozide and PROZAC [*see Contraindications (4)*].

*Thioridazine* — Thioridazine should not be administered with PROZAC or within a minimum of 5 weeks after PROZAC has been discontinued [*see Contraindications (4)*].

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25 mg oral dose of thioridazine produced a 2.4-fold higher C<sub>max</sub> and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs which inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine.

Thioridazine administration produces a dose-related prolongation of the QT<sub>c</sub> interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism.

*Drugs Metabolized by CYP2D6* — Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see list below) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of poor metabolizers. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued [*see Contraindications (4)*].

*Tricyclic Antidepressants (TCAs)* — In 2 studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for 3 weeks or longer after fluoxetine is discontinued. Thus, the dose of TCAs may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued [*see Clinical Pharmacology (12.3)*].

*Benzodiazepines* — The half-life of concurrently administered diazepam may be prolonged in some patients [*see Clinical Pharmacology (12.3)*]. Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

*Antipsychotics* — Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between SSRIs and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine [*see Contraindications (4)*].

*Anticonvulsants* — Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

*Lithium* — There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

*Drugs Tightly Bound to Plasma Proteins* — Because fluoxetine is tightly bound to plasma proteins, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect [*see Clinical Pharmacology (12.3)*].

*Drugs Metabolized by CYP3A4* — In an in vivo interaction study involving coadministration of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine.

Additionally, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

*Olanzapine*— Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

When using PROZAC and olanzapine and in combination, also refer to the Drug Interactions section of the package insert for Symbyax.

## 8 USE IN SPECIFIC POPULATIONS

When using PROZAC and olanzapine in combination, also refer to the Use in Specific Populations section of the package insert for Symbyax.

### 8.1 Pregnancy

*Pregnancy Category C* — PROZAC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure.

*Treatment of Pregnant Women during the First Trimester* — There are no adequate and well-controlled clinical studies on the use of fluoxetine in pregnant women. Results of a number of published epidemiological studies assessing the risk of fluoxetine exposure during the first trimester of pregnancy have demonstrated inconsistent results. More than 10 cohort studies and case-control studies failed to demonstrate an increased risk for congenital malformations overall. However, one prospective cohort study conducted by the European Network of Teratology Information Services reported an increased risk of cardiovascular malformations in infants born to women (N = 253) exposed to fluoxetine during the first trimester of pregnancy compared to infants of women (N = 1,359) who were not exposed to fluoxetine. There was no specific pattern of cardiovascular malformations. Overall, however, a causal relationship has not been established.

*Treatment of Pregnant Women during the Third Trimester* — Neonates exposed to PROZAC, SNRIs, or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SNRIs and SSRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome.

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

*Clinical Considerations* — When treating pregnant women with PROZAC, the physician should carefully consider both the potential risks and potential benefits of treatment, taking into account the risk of untreated depression during pregnancy. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

The physician may consider tapering PROZAC in the third trimester [see *Dosage and Administration* (2.7)].

*Animal Data* — In embryo-fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of fluoxetine at doses up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times, respectively, the maximum recommended human dose (MRHD) of 80 mg on a mg/m<sup>2</sup> basis) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m<sup>2</sup> basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m<sup>2</sup> basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m<sup>2</sup> basis).

### 8.2 Labor and Delivery

The effect of PROZAC on labor and delivery in humans is unknown. However, because fluoxetine crosses the placenta and because of the possibility that fluoxetine may have adverse effects on the newborn, fluoxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

### 8.3 Nursing Mothers

Because PROZAC is excreted in human milk, nursing while on PROZAC is not recommended. In one breast-milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on PROZAC developed crying, sleep

disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

#### 8.4 Pediatric Use

The efficacy of PROZAC for the treatment of Major Depressive Disorder was demonstrated in two 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to  $\leq 18$  [*see Clinical Studies (14.1)*].

The efficacy of PROZAC for the treatment of OCD was demonstrated in one 13-week placebo-controlled clinical trial with 103 pediatric outpatients ages 7 to  $< 18$  [*see Clinical Studies (14.2)*].

The safety and effectiveness in pediatric patients  $< 8$  years of age in Major Depressive Disorder and  $< 7$  years of age in OCD have not been established.

Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (ages 6 to  $\leq 18$ ) with Major Depressive Disorder or OCD [*see Clinical Pharmacology (12.3)*].

The acute adverse reaction profiles observed in the 3 studies (N=418 randomized; 228 fluoxetine-treated, 190 placebo-treated) were generally similar to that observed in adult studies with fluoxetine. The longer-term adverse reaction profile observed in the 19-week Major Depressive Disorder study (N=219 randomized; 109 fluoxetine-treated, 110 placebo-treated) was also similar to that observed in adult trials with fluoxetine [*see Adverse Reactions (6.1)*].

Manic reaction, including mania and hypomania, was reported in 6 (1 mania, 5 hypomania) out of 228 (2.6%) fluoxetine-treated patients and in 0 out of 190 (0%) placebo-treated patients. Mania/hypomania led to the discontinuation of 4 (1.8%) fluoxetine-treated patients from the acute phases of the 3 studies combined. Consequently, regular monitoring for the occurrence of mania/hypomania is recommended.

As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, pediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height and 1.1 kg less in weight than subjects treated with placebo. In addition, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels. The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in pediatric patients receiving fluoxetine. [*see Warnings and Precautions (5.6)*].

PROZAC is approved for use in pediatric patients with MDD and OCD [*see Box Warning and Warnings and Precautions (5.1)*]. Anyone considering the use of PROZAC in a child or adolescent must balance the potential risks with the clinical need.

Significant toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine. Some of these effects occurred at clinically relevant exposures.

In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development was delayed at all doses, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dose. At the end of the treatment period, serum levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and hypospermia) was observed at the high dose. When animals were evaluated after a recovery period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased reactivity at all doses and learning deficit at the high dose) and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were found in the high dose group, indicating that the reproductive organ effects seen at the end of treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20 times, respectively, pediatric exposure at the MRD.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg, intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These doses did not affect overall growth (body weight gain or femoral length). The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area ( $\text{mg}/\text{m}^2$ ) basis.

In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increase shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a  $\text{mg}/\text{m}^2$  basis. Because of the early dosing period in this study, the significance of these findings to the approved pediatric use in humans is uncertain.

Safety and effectiveness of PROZAC and olanzapine in combination in patients less than 18 years of age have not been established.

## 8.5 Geriatric Use

US fluoxetine clinical trials included 687 patients  $\geq 65$  years of age and 93 patients  $\geq 75$  years of age. The efficacy in geriatric patients has been established [see *Clinical Studies (14.1)*]. For pharmacokinetic information in geriatric patients, [see *Clinical Pharmacology (12.4)*]. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SNRIs and SSRIs, including fluoxetine, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction [see *Warnings and Precautions (5.8)*].

Clinical studies of olanzapine and fluoxetine in combination did not include sufficient numbers of patients  $\geq 65$  years of age to determine whether they respond differently from younger patients.

## 8.6 Hepatic Impairment

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose of fluoxetine should be used in patients with cirrhosis. Caution is advised when using PROZAC in patients with diseases or conditions that could affect its metabolism [see *Dosage and Administration (2.7)* and *Clinical Pharmacology (12.4)*].

## 9 DRUG ABUSE AND DEPENDENCE

### 9.3 Dependence

PROZAC has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with PROZAC did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of PROZAC (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

## 10 OVERDOSAGE

### 10.1 Human Experience

Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine hydrochloride, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdosage, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdosage were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown outcome. One of the six fatalities was a 9-year-old boy who had a history of OCD, Tourette's syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which was nonlethal.

Other important adverse reactions reported with fluoxetine overdose (single or multiple drugs) include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like reactions, pyrexia, stupor, and syncope.

### 10.2 Animal Experience

Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose. However, animal experiments can provide useful insights into possible treatment strategies.

The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg, respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.

Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose [see *Overdosage (10.3)*].

### 10.3 Management of Overdose

Treatment should consist of those general measures employed in the management of overdose with any drug effective in the treatment of Major Depressive Disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluoxetine are known.

A specific caution involves patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation [see *Drug Interactions* (7. 9)].

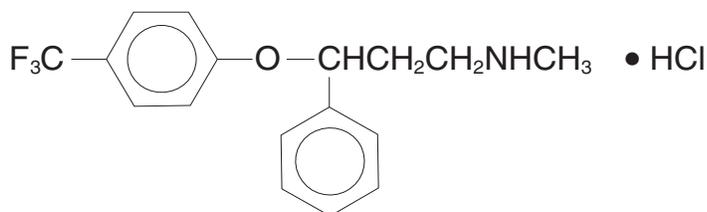
Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

In managing overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*.

For specific information about overdose with olanzapine and fluoxetine in combination, refer to the Overdosage section of the Symbyax package insert.

## 11 DESCRIPTION

PROZAC<sup>®</sup> (fluoxetine capsules, USP) is a selective serotonin reuptake inhibitor for oral administration. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem<sup>®</sup>, fluoxetine hydrochloride). It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of C<sub>17</sub>H<sub>18</sub>F<sub>3</sub>NO•HCl. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Each Pulvule<sup>®</sup> contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol), 20 mg (64.7 μmol), or 40 mg (129.3 μmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and other inactive ingredients. The 10 and 20 mg Pulvules also contain FD&C Blue No. 1, and the 40 mg Pulvule also contains FD&C Blue No. 1 and FD&C Yellow No. 6.

PROZAC Weekly<sup>™</sup> capsules, a delayed-release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 μmol) of fluoxetine. The capsules also contain D&C Yellow No. 10, FD&C Blue No. 2, gelatin, hypromellose, hypromellose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and other inactive ingredients.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Although the exact mechanism of PROZAC is unknown, it is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin.

### 12.2 Pharmacodynamics

Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and α<sub>1</sub>-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

### 12.3 Pharmacokinetics

**Systemic Bioavailability** — In man, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours.

The Pulvule and PROZAC Weekly capsule dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus, fluoxetine may be administered with or without food. PROZAC Weekly capsules, a delayed-release formulation, contain enteric-coated pellets that resist dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. The enteric coating delays the onset of absorption of fluoxetine 1 to 2 hours relative to the immediate-release formulations.

**Protein Binding** — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and  $\alpha_1$ -glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important.

**Enantiomers** — Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

**Metabolism** — Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

**Variability in Metabolism** — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine’s metabolism, like that of a number of other compounds including TCAs and other selective serotonin reuptake inhibitors (SSRIs), involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions [see *Drug Interactions* (7.9)].

**Accumulation and Slow Elimination** — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used [see *Warnings and Precautions* (5.12)]. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine’s metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of PROZAC.

**Weekly Dosing** — Administration of PROZAC Weekly once weekly results in increased fluctuation between peak and trough concentrations of fluoxetine and norfluoxetine compared with once-daily dosing [for fluoxetine: 24% (daily) to 164% (weekly) and for norfluoxetine: 17% (daily) to 43% (weekly)]. Plasma concentrations may not necessarily be predictive of clinical response. Peak concentrations from once-weekly doses of PROZAC Weekly capsules of fluoxetine are in the range of the average concentration for 20 mg once-daily dosing. Average trough concentrations are 76% lower for fluoxetine and 47% lower for norfluoxetine than the concentrations maintained by 20 mg once-daily dosing. Average steady-state concentrations of either once-daily or once-weekly dosing are in relative proportion to the total dose administered. Average steady-state fluoxetine concentrations are approximately 50% lower following the once-weekly regimen compared with the once-daily regimen.

$C_{max}$  for fluoxetine following the 90 mg dose was approximately 1.7-fold higher than the  $C_{max}$  value for the established 20 mg once-daily regimen following transition the next day to the once-weekly regimen. In contrast, when the first 90 mg once-weekly dose and the last 20 mg once-daily dose were separated by 1 week,  $C_{max}$  values were similar. Also, there was a transient increase in the average steady-state concentrations of fluoxetine observed following transition the next day to the once-weekly regimen. From a pharmacokinetic perspective, it may be better to separate the first 90 mg weekly dose and the last 20 mg once-daily dose by 1 week [see *Dosage and Administration* (2.1)].

#### 12.4 Specific Populations

**Liver Disease** — As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used [see *Dosage and Administration* (2.7), *Use in Specific Populations* (8.6)].

**Renal Disease** — In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

**Geriatric Pharmacokinetics** — The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were  $209.3 \pm 85.7$  ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse reactions was observed in those elderly patients.

**Pediatric Pharmacokinetics (children and adolescents)** — Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (10 children ages 6 to <13, 11 adolescents ages 13 to <18) diagnosed with Major Depressive Disorder or Obsessive Compulsive Disorder (OCD). Fluoxetine 20 mg/day was administered for up to 62 days. The average steady-state concentrations of fluoxetine in these children were 2-fold higher than in adolescents (171 and 86 ng/mL, respectively). The average norfluoxetine steady-state concentrations in these children were 1.5-fold higher than in adolescents (195 and 113 ng/mL, respectively). These differences can be almost entirely explained by differences in weight. No gender-associated difference in fluoxetine pharmacokinetics was observed. Similar ranges of fluoxetine and norfluoxetine plasma concentrations were observed in another study in 94 pediatric patients (ages 8 to <18) diagnosed with Major Depressive Disorder.

Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenicity** — The dietary administration of fluoxetine to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day, respectively [approximately 1.2 and 0.7 times, respectively, the maximum recommended human dose (MRHD) of 80 mg on a  $\text{mg}/\text{m}^2$  basis], produced no evidence of carcinogenicity.

**Mutagenicity** — Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

**Impairment of Fertility** — Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a  $\text{mg}/\text{m}^2$  basis) indicated that fluoxetine had no adverse effects on fertility. However, adverse effects on fertility were seen when juvenile rats were treated with fluoxetine [see *Use in Specific Populations (8.4)*].

### 13.2 Animal Toxicology and/or Pharmacology

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

## 14 CLINICAL STUDIES

*When using PROZAC and olanzapine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.*

### 14.1 Major Depressive Disorder

#### Daily Dosing

**Adult** — The efficacy of PROZAC was studied in 5- and 6-week placebo-controlled trials with depressed adult and geriatric outpatients (≥18 years of age) whose diagnoses corresponded most closely to the DSM-III (currently DSM-IV) category of Major Depressive Disorder. PROZAC was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). PROZAC was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

Two 6-week controlled studies (N=671, randomized) comparing PROZAC 20 mg and placebo have shown PROZAC 20 mg daily to be effective in the treatment of elderly patients (≥60 years of age) with Major Depressive Disorder. In these studies, PROZAC produced a significantly higher rate of response and remission as defined, respectively, by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of ≤8. PROZAC was well tolerated and the rate of treatment discontinuations due to adverse reactions did not differ between PROZAC (12%) and placebo (9%).

A study was conducted involving depressed outpatients who had responded (modified HAMD-17 score of ≤7 during each of the last 3 weeks of open-label treatment and absence of Major Depressive Disorder by DSM-III-R criteria) by the end of an initial 12-week open-treatment phase on PROZAC 20 mg/day. These patients (N=298) were randomized to continuation on double-blind

PROZAC 20 mg/day or placebo. At 38 weeks (50 weeks total), a statistically significantly lower relapse rate (defined as symptoms sufficient to meet a diagnosis of Major Depressive Disorder for 2 weeks or a modified HAMD-17 score of  $\geq 14$  for 3 weeks) was observed for patients taking PROZAC compared with those on placebo.

*Pediatric (children and adolescents)* — The efficacy of PROZAC 20 mg/day in children and adolescents (N=315 randomized; 170 children ages 8 to <13, 145 adolescents ages 13 to  $\leq 18$ ) was studied in two 8- to 9-week placebo-controlled clinical trials in depressed outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of Major Depressive Disorder.

In both studies independently, PROZAC produced a statistically significantly greater mean change on the Childhood Depression Rating Scale-Revised (CDRS-R) total score from baseline to endpoint than did placebo.

Subgroup analyses on the CDRS-R total score did not suggest any differential responsiveness on the basis of age or gender.

#### *Weekly dosing for Maintenance/Continuation Treatment*

A longer-term study was conducted involving adult outpatients meeting DSM-IV criteria for Major Depressive Disorder who had responded (defined as having a modified HAMD-17 score of  $\leq 9$ , a CGI-Severity rating of  $\leq 2$ , and no longer meeting criteria for Major Depressive Disorder) for 3 consecutive weeks at the end of 13 weeks of open-label treatment with PROZAC 20 mg once daily. These patients were randomized to double-blind, once-weekly continuation treatment with PROZAC Weekly, PROZAC 20 mg once daily, or placebo. PROZAC Weekly once weekly and PROZAC 20 mg once daily demonstrated superior efficacy (having a significantly longer time to relapse of depressive symptoms) compared with placebo for a period of 25 weeks. However, the equivalence of these 2 treatments during continuation therapy has not been established.

## 14.2 Obsessive Compulsive Disorder

*Adult* — The effectiveness of PROZAC for the treatment of Obsessive Compulsive Disorder (OCD) was demonstrated in two 13-week, multicenter, parallel group studies (Studies 1 and 2) of adult outpatients who received fixed PROZAC doses of 20, 40, or 60 mg/day (on a once-a-day schedule, in the morning) or placebo. Patients in both studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS, total score) ranging from 22 to 26. In Study 1, patients receiving PROZAC experienced mean reductions of approximately 4 to 6 units on the YBOCS total score, compared with a 1-unit reduction for placebo patients. In Study 2, patients receiving PROZAC experienced mean reductions of approximately 4 to 9 units on the YBOCS total score, compared with a 1-unit reduction for placebo patients. While there was no indication of a dose-response relationship for effectiveness in Study 1, a dose-response relationship was observed in Study 2, with numerically better responses in the 2 higher dose groups. The following table provides the outcome classification by treatment group on the Clinical Global Impression (CGI) improvement scale for Studies 1 and 2 combined:

**Table 6**

Outcome Classification (%) on CGI Improvement Scale for Completers in Pool of Two OCD Studies				
Outcome Classification	Placebo	PROZAC		
		20 mg	40 mg	60 mg
Worse	8%	0%	0%	0%
No change	64%	41%	33%	29%
Minimally improved	17%	23%	28%	24%
Much improved	8%	28%	27%	28%
Very much improved	3%	8%	12%	19%

Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

*Pediatric (children and adolescents)* — In one 13-week clinical trial in pediatric patients (N=103 randomized; 75 children ages 7 to <13, 28 adolescents ages 13 to <18) with OCD (DSM-IV), patients received PROZAC 10 mg/day for 2 weeks, followed by 20 mg/day for 2 weeks. The dose was then adjusted in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. PROZAC produced a statistically significantly greater mean change from baseline to endpoint than did placebo as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

Subgroup analyses on outcome did not suggest any differential responsiveness on the basis of age or gender.

## 14.3 Bulimia Nervosa

The effectiveness of PROZAC for the treatment of bulimia was demonstrated in two 8-week and one 16-week, multicenter, parallel group studies of adult outpatients meeting DSM-III-R criteria for bulimia. Patients in the 8-week studies received either 20 or 60 mg/day of PROZAC or placebo in the morning. Patients in the 16-week study received a fixed PROZAC dose of 60 mg/day (once a day) or placebo. Patients in these 3 studies had moderate to severe bulimia with median binge-eating and vomiting frequencies ranging from 7 to 10 per week and 5 to 9 per week, respectively. In these 3 studies, PROZAC 60 mg, but not 20 mg, was statistically significantly superior to placebo in reducing the number of binge-eating and vomiting episodes per week. The statistically significantly superior effect of 60 mg versus placebo was present as early as Week 1 and persisted throughout each study. The

PROZAC-related reduction in bulimic episodes appeared to be independent of baseline depression as assessed by the Hamilton Depression Rating Scale. In each of these 3 studies, the treatment effect, as measured by differences between PROZAC 60 mg and placebo on median reduction from baseline in frequency of bulimic behaviors at endpoint, ranged from 1 to 2 episodes per week for binge-eating and 2 to 4 episodes per week for vomiting. The size of the effect was related to baseline frequency, with greater reductions seen in patients with higher baseline frequencies. Although some patients achieved freedom from binge-eating and purging as a result of treatment, for the majority, the benefit was a partial reduction in the frequency of binge-eating and purging.

In a longer-term trial, 150 patients meeting DSM-IV criteria for Bulimia Nervosa, purging subtype, who had responded during a single-blind, 8-week acute treatment phase with PROZAC 60 mg/day, were randomized to continuation of PROZAC 60 mg/day or placebo, for up to 52 weeks of observation for relapse. Response during the single-blind phase was defined by having achieved at least a 50% decrease in vomiting frequency compared with baseline. Relapse during the double-blind phase was defined as a persistent return to baseline vomiting frequency or physician judgment that the patient had relapsed. Patients receiving continued PROZAC 60 mg/day experienced a significantly longer time to relapse over the subsequent 52 weeks compared with those receiving placebo.

#### 14.4 Panic Disorder

The effectiveness of PROZAC in the treatment of Panic Disorder was demonstrated in 2 double-blind, randomized, placebo-controlled, multicenter studies of adult outpatients who had a primary diagnosis of Panic Disorder (DSM-IV), with or without agoraphobia.

Study 1 (N=180 randomized) was a 12-week flexible-dose study. PROZAC was initiated at 10 mg/day for the first week, after which patients were dosed in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of PROZAC-treated patients were free from panic attacks at endpoint than placebo-treated patients, 42% versus 28%, respectively.

Study 2 (N=214 randomized) was a 12-week flexible-dose study. PROZAC was initiated at 10 mg/day for the first week, after which patients were dosed in a range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of PROZAC-treated patients were free from panic attacks at endpoint than placebo-treated patients, 62% versus 44%, respectively.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

The following products are manufactured by Eli Lilly and Company for Dista Products Company:  
Pulvule are available in 10mg, 20mg and 40mg capsule strengths and packages as follows:

	Pulvule Strength		
	10 mg <sup>1</sup>	20 mg <sup>1</sup>	40 mg <sup>1</sup>
Pulvule No. <sup>2</sup>	PU3104	PU3105	PU3107
Cap Color	Opaque green	Opaque green	Opaque green
Body Color	Opaque green	Opaque yellow	Opaque orange
Identification	DISTA 3104 Prozac 10 mg	DISTA 3105 Prozac 20 mg	DISTA 3107 Prozac 40 mg
<b>NDC Codes:</b>			
Bottles of 30		0777-3105-30	0777-3107-30
Bottles 100	0777-3104-02	0777-3105-02	
Bottles of 2000		0777-3105-07	

The following product is manufactured and distributed by Eli Lilly and Company:

PROZAC<sup>®</sup> Weekly<sup>™</sup> Capsules are available in:

The 90 mg<sup>1</sup> capsule is an opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with Lilly on the cap and 3004 and 90 mg on the body.

NDC 0002-3004-75 (PU3004) – Blister package of 4

<sup>1</sup> Fluoxetine base equivalent.

<sup>2</sup> Protect from light.

### 16.2 Storage and Handling

Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F).

## **17 PATIENT COUNSELING INFORMATION**

*See the FDA-approved Medication Guide.*

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking PROZAC as monotherapy or in combination with olanzapine. When using PROZAC and olanzapine in combination, also refer to the Patient Counseling Information section of the package insert for Symbyax.

### **17.1 General Information**

Healthcare providers should instruct their patients to read the Medication Guide before starting therapy with PROZAC and to reread it each time the prescription is renewed.

Healthcare providers should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with PROZAC and should counsel them in its appropriate use. Healthcare providers should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their healthcare provider if these occur while taking PROZAC.

*When using PROZAC and olanzapine in combination, also refer to the Medication Guide for Symbyax.*

### **17.2 Clinical Worsening and Suicide Risk**

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [*see Box Warning and Warnings and Precautions (5.1)*].

### **17.3 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions**

Patients should be cautioned about the risk of serotonin syndrome or NMS-like reactions with the concomitant use of PROZAC and triptans, tramadol, or other serotonergic agents [*see Warnings and Precautions (5.2) and Drug Interactions (7.3)*].

Patients should be advised of the signs and symptoms associated with serotonin syndrome or NMS-like reactions that may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, in which the symptoms may include hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be cautioned to seek medical care immediately if they experience these symptoms.

### **17.4 Allergic Reactions and Rash**

Patients should be advised to notify their physician if they develop a rash or hives [*see Warnings and Precautions (5.3)*]. Patients should also be advised of the signs and symptoms associated with a severe allergic reaction, including swelling of the face, eyes, or mouth, or have trouble breathing. Patients should be cautioned to seek medical care immediately if they experience these symptoms.

### **17.5 Abnormal Bleeding**

Patients should be cautioned about the concomitant use of fluoxetine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents have been associated with an increased risk of bleeding [*see Warnings and Precautions (5.7) and Drug Interactions (7.6)*]. Patients should be advised to call their doctor if they experience any increased or unusual bruising or bleeding while taking PROZAC.

### **17.6 Hyponatremia**

Patients should be advised that hyponatremia has been reported as a result of treatment with SNRIs and SSRIs, including PROZAC. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death [*see Warnings and Precautions (5.8)*].

### **17.7 Potential for Cognitive and Motor Impairment**

PROZAC may impair judgment, thinking, or motor skills. Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected [*see Warnings and Precautions (5.11)*].

### **17.8 Use of Concomitant Medications**

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription medication, including Symbyax, Sarafem, or over-the-counter drugs, including herbal supplements or alcohol. Patients should also be advised to inform their physicians if they plan to discontinue any medications they are taking while on PROZAC.

#### **17.9 Discontinuation of Treatment**

Patients should be advised to take PROZAC exactly as prescribed, and to continue taking PROZAC as prescribed even after their symptoms improve. Patients should be advised that they should not alter their dosing regimen, or stop taking PROZAC without consulting their physician [see *Warnings and Precautions (5.13)*]. Patients should be advised to consult with their healthcare provider if their symptoms do not improve with PROZAC.

#### **17.10 Use in Specific Populations**

*Pregnancy* — Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Prozac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [see *Use in Specific Populations (8.1)*].

*Nursing Mothers* — Patients should be advised to notify their physician if they intend to breast-feed an infant during therapy. Because PROZAC is excreted in human milk, nursing while taking PROZAC is not recommended [see *Use in Specific Populations (8.3)*].

*Pediatric Use* — PROZAC is approved for use in pediatric patients with MDD and OCD [see *Box Warning and Warnings and Precautions (5.1)*]. Limited evidence is available concerning the longer-term effects of fluoxetine on the development and maturation of children and adolescent patients. Height and weight should be monitored periodically in pediatric patients receiving fluoxetine. Safety and effectiveness of PROZAC and olanzapine in combination in patients less than 18 years of age have not been established [see *Warnings and Precautions (5.6) and Use in Specific Populations (8.4)*].

Literature revised Month dd, yyyy

**Eli Lilly and Company, Indianapolis, IN 46285, USA**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**NDA 18-936/S-093**

**NDA 21-235/S-016**

**SUMMARY REVIEW**

**REGULATORY PROJECT MANAGER  
LABELING REVIEW**

Date: March 25, 2011  
 DRUG/NDA: Prozac (fluoxetine HCL) Capsules (NDA 018936) & Prozac (fluoxetine HCL) weekly Capsules (NDA 021235)  
 Sponsor: Eli Lilly & Co.  
 Indication: MDD  
 Supplements:

<b>NDA</b>	<b>Supplement</b>	<b>Dated</b>	<b>Action</b>
<b>Prozac (fluoxetine HCl) Capsules (NDA 018936)</b>			
018936	S-075/S-077	3-1-06, 9-29-06	AP Letter Dated 3-19-09
018936	S-091/S-093 /S-095	5-21-09, 11-6-09, 4-14-10	Open
<b>Prozac (fluoxetine HCl) Weekly Capsules (NDA 021235)</b>			
021235	S-014	12-23-08	AP Letter Dated 1-30-09
021235	S-015/S-016 /S-017	5-21-09, 11-6-09, 4-14-10	Open

**NOTES**

- Both Prozac capsules and Prozac Weekly share the same labeling. Therefore, I used the last approved labeling, for comparison purposes, attached to the 3-19-09 approval letter for supplements 018936/S-075 & 018936/S-077.

**REVIEW**

**018936/S-091**

**021235/S-015**

**Date: 5-21-09 and amended on 11-12-09, 9-13-10, 3-23-11, and 3-25-11**

**CBE: No, Prior Approval**

**Reviewed by Medical Officer: Yes (reviews dated 11-16-09 [Hearst], and 11-12-10 [Levin])**

These supplements provide for the following changes to product labeling:

1. Revisions to Section 6.2 (Other Reactions)

- Addition of 4 new Medical Dictionary of Regulatory Activities (MedDRA) adverse reaction (AR) terms (i.e. Balance Disorder, Bruxism, Gynecological Bleeding, and Hypotension)
- Reinstatement of 3 AR terms (i.e. Alopecia, Dysuria, and Micturition Disorder)
- Inclusion of the adverse event term depersonalization

2. The supplements also provided for the following minor additional changes:

- Deletion of “have not been established” at the end of Section 2.6
- Revisions to Description Data Source in Sections 5.3, 5.4, 5.5, and 6.1
- Minor editorial changes

These minor changes are acceptable and the sponsor has properly implemented them as changes described in an annual report as stipulated under 21 CFR 314.70(d).

**018936/S-093**

**021235/S-016**

**Date: 11-6-09, and amended on 3-25-11**

**CBE: Yes**

**Reviewed by Medical Officer: Yes (reviews dated 4-20-10 [OSE], 6-14-10 [PMHT], and 3-27-11 [Levin])**

These supplements provide for the following changes:

1. Revision to Section 8.1 (Pregnancy) to add a statement to the Pregnancy section of the Prozac (fluoxetine) label that (b) (4) a potential risk of cardiovascular defects in infants of women who were exposed to fluoxetine during the first trimester of pregnancy.
2. Deletion of label language from Prozac USPI and Medication Guide related to the discontinued Prozac Oral Solution

**018936/S-095**

**021235/S-017**

**Date: 4-14-10 and amended on 10-22-10**

**CBE: No, Prior Approval**

**Reviewed by Medical Officer: Yes (review dated 3-9-11 [Levin])**

These supplements provide for a comprehensive Medication Guide (MG) as requested by the Agency in an e-mail dated 3-15-10. The Agency subsequently issued a complete response letter to these supplements dated 9-24-10, requesting additional changes to the MG due to our updated comprehensive MG template.

Lilly incorporated all of our revisions, and they were found to be acceptable by the medical officer.

The only revision that Lilly did not incorporate was to provide the MG in 2 column format.

## **CONCLUSIONS**

1. The above labeling supplements only provide for those revisions as stated above for these open supplements when compared to the last approved labeling (approval letter dated 3-19-09).
2. Given that the sponsor has incorporated our changes, when we attained agreement via email on 3-22-11 as well as accepted the recommendations conveyed in our 9-24-11 CR letter, I recommend that this review, along with the corresponding reviews for these supplements, be sufficient to approve these supplemental applications.

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Kofi Ansah, Pharm.D., Senior Regulatory Project Manager

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Paul David, R.Ph., CPMS

Enclosure: Annotated labeling changes

32 Pages Immediately Following Withheld - b(4) Draft Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KOFI B ANSAH  
03/31/2011

PAUL A DAVID  
04/01/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 18-936/S-093**

**NDA 21-235/S-016**

**MEDICAL REVIEW(S)**

<b>NDA Supplements:</b>	18-936/S093 and 21-235/S016
<b>Sponsor:</b>	Eli Lilly
<b>Drug:</b>	Prozac and Prozac Weekly (fluoxetine)
<b>Type of Submission:</b>	Changes Being Effected Labeling Supplement
<b>Date of Submission:</b>	November 6, 2010
<b>Recommended Action:</b>	Approval

## 1. Introduction

Eli Lilly and Company submitted a Changes Being Effective (CBE) Labeling Supplement on November 6, 2009 in which they added a statement to the Pregnancy section of the Prozac (fluoxetine) label that [REDACTED] (b) (4) a potential risk of cardiovascular defects in infants of women who were exposed to fluoxetine during the first trimester of pregnancy. In addition to the CBE, the sponsor submitted a justification document to support their labeling change. The submission states that the sponsor conducted a meta-analysis of available epidemiological data regarding the potential effects of first trimester fluoxetine exposure and the potential risk of congenital malformations, with a particular focus on cardiac defects in response to a request by the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA). The meta-analysis is entitled: "Analysis, Results, and Label Language Proposal following a Meta-Analysis of Published Epidemiological Studies to Assess the Effect of Fluoxetine Exposure During the First Trimester of Pregnancy and the Risk of Major Malformations.

The Division consulted The Office of Surveillance and Epidemiology and the Maternal Health Team for their assessment of the meta-analysis and proposed labeling. Both found that the meta-analysis had substantial problems [REDACTED] (b) (4) [REDACTED] the teams thought that one of the epidemiological studies had merit and would support the addition of language about first trimester exposure to fluoxetine and a potentially increased risk of cardiovascular abnormalities in children exposed to fluoxetine in the first trimester.

## 2. Summary of OSE Review

Fatmatta Kuyateh, M.D., M.S., Medical Officer, Division of Epidemiology (DEPI), Office of Surveillance and Epidemiology (OSE) performed a consultative review (April 20, 2010). DEPI incorporated into this review of the meta-analysis report, methodology and results information obtained from a qualitative assessment of the individual studies included in the meta-analysis, and a feasibility assessment of conducting the meta-analysis, both provided by Lilly.

The meta-analysis included eight published observational studies. The results of the meta-analysis suggest an increased risk of major congenital anomalies in infants born to women who were exposed to fluoxetine during the first trimester of pregnancy compared

to women who did not use fluoxetine during pregnancy, although the association was not statistically significant [OR=1.34; 95% CI (0.98-1.83)]. The results also suggest a nearly 3-fold increased risk of cardiovascular defects among infants born to women who used fluoxetine during the first trimester of pregnancy compared to women who did not use fluoxetine during pregnancy (OR: 2.92; 95%CI 1.29 – 6.58). Based on further post-hoc analyses that analyzed only the non-cardiac malformation data, the sponsor concluded that the positive point estimates for major malformations were driven by cardiovascular defects.

Dr. Kuyateh notes that regarding the quality of the meta-analysis, the study design was appropriate for the stated objectives, heterogeneity and publication bias were evaluated, and extensive analyses were conducted including primary analyses, sensitivity analyses, and post-hoc analyses. However, only published studies in English were included and no confounders were controlled for, thus severely limiting the interpretation of the results. Other limitations include potential misclassification of outcome and variations in exposure definitions.

DEPI's review of the meta-analysis and the individual constituent studies found trends towards an increased risk of major congenital malformations in infants of women who used fluoxetine during the first trimester of pregnancy. The results of the meta-analysis support previous findings by Diav-Citrin et al.<sup>3</sup> of an increased risk of cardiovascular defects among infants of women who used fluoxetine during the first trimester of pregnancy. However, because of unadjusted confounding, the results of this meta-analysis do not provide definitive information to support any direct or causal associations. Thus DEPI concludes that the findings of this meta-analysis alone are not sufficient to implement the labeling changes proposed by Eli Lilly. Further evaluation of the individual studies may provide more useful information for implementing any regulatory action concerning fluoxetine and major congenital malformations or congenital heart defects.

### **3. Summary of the Maternal Health Team Review**

Leyla Sahin, M.D, Medical Officer, Maternal Health Team performed the consult review (June 6, 2010)

Dr. Sahin reviewed the individual studies included in the sponsor's meta-analysis as well as other prospective and retrospective epidemiologic data. Dr. Sahin noted that all of the studies have limitations such as insufficient power, inability to confirm exposure, variations in outcome definition, and/or lack of control of confounders. The MHT did not find conclusive evidence that fluoxetine increases the risk of congenital malformations overall or cardiovascular malformations, with the exception of one prospective cohort study that suggests a potential risk of cardiovascular defects in infants of women exposed to fluoxetine during the first trimester of pregnancy compared to infants of women who were not exposed to fluoxetine. The MHT recommends changing labeling to reflect these findings.

Dr. Sahin provided the following additional comments:

As safety data regarding use of SSRIs in pregnancy have emerged, labeling of all SSRIs and selective norepinephrine re-uptake inhibitors (SNRIs) has been updated to include data on the risks of neonatal withdrawal syndrome (2004), persistent pulmonary hypertension in the newborn (2007), and risk of relapse of depression during pregnancy (2007). All of the SSRI and SNRI drugs, except for paroxetine, are labeled with pregnancy category C based on positive reproductive toxicology study results in animal studies and a lack of adequate human data. Paroxetine is the only SSRI labeled as a pregnancy category D based on human data supporting an increased risk of major congenital cardiac malformations with first trimester exposure to paroxetine.

Between 14% and 23% of pregnant women will experience a depressive disorder while pregnant<sup>1</sup>. Depression during pregnancy is associated with increased risks of adverse consequences for both mother and baby including: preterm delivery, low birth weight, preeclampsia, and postpartum depression<sup>2</sup>. These women may also be more likely to smoke, drink alcohol, use illicit drugs, and experience social withdrawal and suicidal ideation. Untreated depression may contribute to higher rates of therapeutic abortions, relapse of depressive symptoms, noncompliance with prenatal care, poor maternal weight gain, and overall perinatal and psychosocial complications for the baby<sup>3</sup>.

Many patients with mild-to-moderate depression can be managed using psychosocial approaches, including individual and group psychotherapy. Pregnant women with depression require individualized therapy but many also require concomitant treatment with an antidepressant. SSRIs are the most frequently prescribed class of antidepressant. In 2003, approximately 13% of women took an antidepressant at some point in pregnancy, a rate that has doubled since 1999<sup>4</sup>.

Women who have a personal history of severe, recurrent depression (even if currently asymptomatic or minimally symptomatic) are at high risk of relapse if medication is discontinued. In one prospective cohort study of women who suffered from recurrent depression, the risk of relapse was six-fold higher among women who elected to discontinue antidepressant treatment in pregnancy

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<sup>1</sup> Gaynes BN, et al. Perinatal depression: prevalence, screening accuracy and screening outcomes. *Evid Rep/Technol*

Assess (Summ) 2005:1–8.

<sup>2</sup> Way CM. Safety of Newer Antidepressants in Pregnancy. *Pharmacotherapy*. 2007 Apr; 27(4): 546-52.

<sup>3</sup> Berard A, Ramos E, Rey E, Blais L, St.-Andre M et al. First trimester exposure to paroxetine and risk of cardiac

malformation in infants: the importance of dosage. *Birth Defects Res B Dev Reprod Toxicol*. 2007 Feb; 80(1):

18-27.

<sup>4</sup> Cooper WO, Pont ME, Ray WA. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol* 2007;196:544.e1.

compared to women who continued treatment at the same dose throughout pregnancy<sup>5</sup>.

#### **4. Labeling**

##### **4.1 Sponsor's proposed labeling:**



##### **4.2 Maternal Health Team's Proposed Labeling**



##### **4.3 Final Language Agreed Upon with the Sponsor**

*Treatment of Pregnant Women during the First Trimester* — There are no adequate and well-controlled clinical studies on the use of fluoxetine in pregnant women. Results of a number of published epidemiological studies assessing the risk of fluoxetine exposure during the first trimester of pregnancy have demonstrated inconsistent results. More than 10 cohort studies and case-control studies failed to

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<sup>5</sup> Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006 Feb 1; 295(5): 499-507.

demonstrate an increased risk for congenital malformations overall. However, one prospective cohort study conducted by the European Network of Teratology Information Services reported an increased risk of cardiovascular malformations in infants born to women (N = 253) exposed to fluoxetine during the first trimester of pregnancy compared to infants of women (N = 1,359) who were not exposed to fluoxetine. There was no specific pattern of cardiovascular malformations. Overall, however, a causal relationship has not been established.

## **5. Conclusions and Recommendations**

The sponsor has provided evidence from epidemiological evidence that there may be a potential increased risk of cardiovascular malformations in infants born to women exposed to fluoxetine during the first trimester of pregnancy. DEPI and MHT agree that although the sponsor's meta-analysis does not support these conclusions, one prospective cohort study (which was included in the meta-analysis) does support the finding. DEPI, OSE, and the Division of Psychiatry Products have agreed on the final labeling that was negotiated with the sponsor.

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/s/  
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ROBERT L LEVIN  
03/27/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 18-936/S-093**

**NDA 21-235/S-016**

**OTHER REVIEW(S)**



Pediatric and Maternal Health Staff  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

### **MATERNAL HEALTH TEAM (MHT) REVIEW**

**Date:** 06-09-2010 **Date Consulted:** 12-21-2009

**From:** Leyla Sahin, M.D.  
Medical Officer, Maternal Health Team

**Through:** Karen B. Feibus, M.D.  
Medical Team Leader, Maternal Health Team

**Through:** Lisa Mathis, M.D.  
Associate Director, Office of New Drugs  
Pediatric and Maternal Health Staff

**To:** Division of Psychiatry Products

**Drug:** Prozac (fluoxetine), NDA 018936/SLR-020

**Subject:** Sponsor's proposed Pregnancy Labeling change regarding increased risk of cardiovascular malformations in children who were exposed to fluoxetine in-utero

**Materials Reviewed:** Eli Lilly's submission, PubMed literature review

**Consult Question:** DPP would like your input on the sponsor's proposed labeling change.

## **EXECUTIVE SUMMARY**

Depression during pregnancy is a serious and potentially life-threatening medical condition that often requires pharmacotherapy.

The sponsor's proposed Pregnancy labeling change for Prozac states (b) (4) a potential risk of cardiovascular defects in infants of women who were exposed to fluoxetine during the first trimester of pregnancy. The Office of Surveillance and Epidemiology (OSE) Division of Epidemiology (DEPI) reviewed the sponsor's meta-analysis and concluded that the validity of the meta-analysis is limited, as the study was unable to control for confounders, (b) (4)

The Maternal Health Team reviewed the individual studies included in the sponsor's meta-analysis as well as other prospective and retrospective epidemiologic data. All of the studies have limitations such as insufficient power, inability to confirm exposure, variations in outcome definition, and/or lack of control of confounders. The MHT did not find conclusive evidence that fluoxetine increases the risk of congenital malformations overall or cardiovascular malformations, with the exception of one prospective cohort study that suggests a potential risk of cardiovascular defects in infants of women exposed to fluoxetine during the first trimester of pregnancy compared to infants of women who were not exposed to fluoxetine. The MHT recommends changing labeling to reflect these findings.

## **INTRODUCTION**

Eli Lilly and Company (Lilly) submitted a Changes Being Effective (CBE) Labeling Supplement on November 6, 2009 in which they added a statement to the Pregnancy section of the Prozac (fluoxetine) label that (b) (4) a potential risk of cardiovascular defects in infants of women who were exposed to fluoxetine during the first trimester of pregnancy. In addition to the CBE, the sponsor submitted a justification document to support their labeling change. The submission states that the sponsor conducted a meta-analysis of available epidemiological data regarding the potential effects of first trimester fluoxetine exposure and the potential risk of congenital malformations, with a particular focus on cardiac defects in response to a request by the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA).

The DPP asked MHT to review the sponsor's labeling change and their supporting document. This review provides a response to the sponsor's labeling change and a review of the literature regarding fluoxetine exposure during pregnancy and congenital malformations, including cardiovascular malformations. Please see OSE DEPI reviewer, Dr. Fatmatta Kuyateh's review of the sponsor's meta-analysis.

## **BACKGROUND**

Prozac (fluoxetine) is a selective serotonin re-uptake inhibitor (SSRI) that was approved for the treatment of depression by the FDA in 1987. Since Prozac's initial approval, its approved indications have expanded to include obsessive compulsive disorder, bulimia, and panic disorder. As safety data regarding use of SSRIs in pregnancy have emerged, labeling of all SSRIs and selective norepinephrine re-uptake inhibitors (SNRIs) has been updated to include data on the risks of neonatal withdrawal syndrome (2004), persistent pulmonary hypertension in the newborn (2007), and risk of relapse of depression during pregnancy (2007). All of the SSRI and SNRI drugs, except for paroxetine, are labeled with pregnancy category C based on positive reproductive toxicology study results in animal studies and a lack of adequate human data. Paroxetine is the only SSRI labeled as a pregnancy category D based on human data supporting an increased risk of major congenital cardiac malformations with first trimester exposure to paroxetine.

Between 14% and 23% of pregnant women will experience a depressive disorder while pregnant<sup>1</sup>. Depression during pregnancy is associated with increased risks of adverse consequences for both mother and baby including: preterm delivery, low birth weight, preeclampsia, and postpartum depression<sup>2</sup>. These women may also be more likely to smoke, drink alcohol, use illicit drugs, and experience social withdrawal and suicidal ideation. Untreated depression may contribute to higher rates of therapeutic abortions, relapse of depressive symptoms, noncompliance with prenatal care, poor maternal weight gain, and overall perinatal and psychosocial complications for the baby<sup>3</sup>.

Many patients with mild-to-moderate depression can be managed using psychosocial approaches, including individual and group psychotherapy. Pregnant women with depression require individualized therapy but many also require concomitant treatment with an antidepressant. SSRIs are the most frequently prescribed class of antidepressant. In 2003, approximately 13% of women took an antidepressant at some point in pregnancy, a rate that has doubled since 1999<sup>4</sup>.

Women who have a personal history of severe, recurrent depression (even if currently asymptomatic or minimally symptomatic) are at high risk of relapse if medication is discontinued. In one prospective cohort study of women who suffered from recurrent depression, the risk of relapse was six-fold higher among women who elected to discontinue antidepressant treatment in pregnancy compared to women who continued treatment at the same dose throughout pregnancy<sup>5</sup>.

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<sup>1</sup> Gaynes BN, et al. Perinatal depression: prevalence, screening accuracy and screening outcomes. *Evid Rep/Technol Assess (Summ)* 2005:1–8.

<sup>2</sup> Way CM. Safety of Newer Antidepressants in Pregnancy. *Pharmacotherapy*. 2007 Apr; 27(4): 546-52.

<sup>3</sup> Berard A, Ramos E, Rey E, Blais L, St.-Andre M et al. First trimester exposure to paroxetine and risk of cardiac malformation in infants: the importance of dosage. *Birth Defects Res B Dev Reprod Toxicol*. 2007 Feb; 80(1): 18-27.

<sup>4</sup> Cooper WO, Pont ME, Ray WA. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol* 2007;196:544.e1.

<sup>5</sup> Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA*. 2006 Feb 1; 295(5): 499-507.

## MATERIALS REVIEWED

- Eli Lilly's Fluoxetine Exposure During the First Trimester of Pregnancy and the Risk of Major Congenital Malformations: A qualitative Literature Review of Epidemiological Studies
- Eli Lilly's Analysis, Results, and Label Language Proposal following a Meta-Analysis of Published Epidemiological Studies to Assess the Effect of Fluoxetine Exposure During the First Trimester of Pregnancy and the Risk of Major Malformations
- OSE's Division of Epidemiology Review of Eli Lilly's meta-analysis (dated 4-20-2010)
- MHT's review of the published literature on the risk of congenital malformations in infants with in-utero exposure to SSRIs (dated 7-20-2007)
- Einarson A, Choi J, Einarson TR, Koren G. 2009. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry*. 54(4):242-246.
- Diav-Citrin O, Shechtman S, Weinbaum D, Wajnberg R, Avgil M, Di Gianantonio E, Clementi M, Weber-Schoendorfer C, Schaefer C, Ornoy A. 2008. Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study. *Br J Clin Pharmacol* 66(5):695-705.
- Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth Outcomes in Pregnant Women Taking Fluoxetine. *N Engl J Med* 1996; 335:1010-1015.
- Pastuszak A, Schick-Boschetto B, Zuber C, Feldkamp M, Pinelli M, Sihh S, Donnenfeld A, McCormack M, Leen-Mitchell M, Woodland C, et al. 1993. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA* 269(17):2246-2248.
- Oberlander TF, Warburton W, Misri S, Riggs W, Aghajanian J, Hertzman C. 2008. Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. *Birth Defects Res B Dev Reprod Toxicol* 83(1):68-76.
- Malm H, Klaukka T, Neuvonen PJ. 2005. Risks associated with selective serotonin reuptake inhibitors in pregnancy. *Obstet Gynecol* 106(6):1289-1296.
- Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM; National Birth Defects Prevention Study 2007. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 356(26):2684-2692.
- Louik C, Lin AE, Werler MM, Hernandez-Diaz S, Mitchell AA 2007 First trimester use of selective serotonin reuptake inhibitors and the risk of birth defects. *N Engl J Med* 356(26):2675-2683.

- Pederson L, Henriksen T, Vestergaard M, Olsen J, Bech B. 2009 Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 23(339): b3569 doi:10.1136/bmj.b3569.
- Merlob P, Birk E, Sirota L, Linder N, Berant M, Stahl B, Klinger G. 2009. Are selective serotonin reuptake inhibitors cardiac teratogens? Echocardiographic screening of newborns with persistent heart murmur. *Birth Defects Res A Clin Mol Teratol* 85(10):837-841.
- Kallen BA, Otterblad P. 2007. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. *Birth Defects Res A Clin Mol Teratol* 79(4):301-308.
- GSK Medicine. Final report on bupropion and other antidepressants, including paroxetine, in pregnancy and the occurrence of cardiovascular and major congenital malformations. GSK Medicine web site. Available at: <http://www.gskclinicalstudyregister.com/files/pdf/3494.pdf>.
- The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists *Obstetrics and Gynecology* 2009.

## REVIEW OF SPONSOR'S SUBMISSION

In response to MHRA's request on 16 March 2009 for a meta-analysis of available epidemiological data regarding the potential effects of first trimester fluoxetine exposure and the potential risk on congenital malformations, Lilly conducted a search of the PubMed and EMBASE literature databases up to April 7, 2009.

For this meta-analysis, only prospective or retrospective cohort studies and case-control studies with an internal comparison group(s) were included. The primary outcome measure was major congenital malformation. Additionally, cardiac defects were examined.

Based on the suitability criteria, the sponsor considered the following nine studies for this review:

- 4 prospective cohort studies:
  - Einarson et al. 2009
  - Diav-Citrin et al. 2008
  - Chambers et al. 1996
  - Pastuszek et al. 1993
- 3 retrospective cohort studies:
  - Oberlander et al. 2008
  - Malm et al. 2005
  - Källén et al. 2007

- 2 case control studies:
  - Alwan et al. 2007
  - Louik et al. 2007

The sponsor gave each study a 27 item quality score based on the Downs and Black scoring system<sup>6</sup>. The quality score was not used for weighting or stratification by the sponsor.

### Meta-Analysis

Eight studies (four prospective cohort studies, two retrospective cohort studies, and two case control studies) met the criteria for inclusion in the meta-analysis. The criteria included the following:

- English publication
- Study in human use
- Nonfluoxetine exposure comparison group
- Cohort or case-control study design
- Provides information regarding fluoxetine use during the first trimester of pregnancy and the occurrence of major malformations/cardiovascular defects.

The meta-analysis criteria excluded reports from the Swedish Registry study (Källén 2007) because of a lack of internal comparator group, and because outcomes included minor malformations. The i3 (United Healthcare) study which used GlaxoSmithKline data was excluded from the meta-analysis because the comparator was exposure to another SSRI. A Danish Registry study<sup>7</sup> was excluded from the meta-analysis because although it provided data on the teratogenic risks of SSRIs in general, it didn't provide data on fluoxetine.

### Meta-Analysis Studies

Study	Included in Meta-Analysis for major malformation	Included in Meta-Analysis for cardiovascular malformation	Reference	Study Design
Study 1	✓		Einarson et al. 2009	Prospective cohort study
Study 2	✓	✓	Diav-Citrin et al. 2008	Prospective cohort study
Study 3	✓	✓	Chambers et al. 1996	Prospective cohort study
Study 4	✓	✓	Pastuszak et al. 1993	Prospective cohort study
Study 5	✓	✓	Oberlander et al. 2008	Retrospective cohort study
Study 6	✓		Malm et al. 2005	Retrospective cohort study
Study 7			Alwan et al. 2007	Case-control study

<sup>6</sup> Downs SH, Black N. 1998. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 52(6):377-384.

<sup>7</sup> Wogelius P, Nørgaard M, Gislum M, Pedersen L, Munk E, Mortensen PB, Lipworth L, Sørensen HT. 2006. Maternal use of selective serotonin reuptake inhibitors and risk of congenital malformations. *Epidemiology* 17:701-704.

**Meta-analysis for Major Malformations**

The primary analysis was conducted on data from Studies 1 through 6. They are all cohort studies for which the outcome was based on disease status (major malformation). Data from case control studies (Studies 7 and 8) were not used in the primary analysis because of differences in study designs and study methods. However, data from Study 7 were used in post-hoc analyses. Study 8 was not included in the post-hoc analysis that evaluated major malformations because it was not possible to extract the exact number of infants exposed to fluoxetine with major malformations, due to multiple counting of infants who had more than one major malformation.

The results of the initial meta-analysis showed that women exposed to fluoxetine during the first trimester of pregnancy did not have a statistically significantly increased risk of delivering a baby affected by a major malformation compared with women not exposed to fluoxetine (OR = 1.34; 95% confidence interval 0.98 to 1.83,  $p=0.062$ ).

A post-hoc analysis analyzed the data from both the cohort studies (Studies 1 through 6) and one case-control study (Study 7). These results from a post hoc analysis reached statistical significance with an OR similar to the meta-analysis (OR = 1.32; 95% CI: 1.05 to 1.66;  $p=.018$ ). Based on these results, the sponsor concluded that the post-hoc analyses indicate an overall trend toward a possible association, but that this association was mainly driven by the increased risk of cardiac defects.

**Meta-analysis for Cardiovascular Defects**

The meta-analysis for cardiovascular defects was conducted on Studies 2 through 5, which were all cohort studies with outcomes based on disease status (cardiac defect). As with major malformations, case control studies (Studies 7 and 8) were not included in the primary analysis of this outcome. Studies 1 and 6 were not included in the analysis of cardiovascular defects due to lack of specific data about cardiovascular defects.

This meta-analysis showed a statistically significant odds ratio for cardiovascular defects in women treated with fluoxetine during the first trimester of pregnancy compared to women not exposed to fluoxetine (primary analysis: OR=2.92; 95% CI: 1.29 to 6.58;  $p=0.025$ ).

However, the post hoc analyses showed variable results:

- cohort studies and case-control studies OR=1.23, 95% CI: 0.60 to 2.53,  $p=0.573$
- cohort studies plus the large Swedish Registry study OR=1.43, 95% CI: 0.83 to 2.47,  $p=0.143$

**Sponsor's Assessment of the Literature**

The sponsor's assessment of the nine epidemiological studies showed that the studies had limitations. Some of these limitations were associated with the particular study design (e.g., recall bias in case-control studies) or were related to the particular methodology used (e.g., lack of control for important confounders). Several studies had low participation rates and utilized small sample sizes. Furthermore, the magnitude and direction of estimated effect sizes of first trimester fluoxetine exposure and the potential risk on congenital malformations were inconsistent. In summary, their qualitative literature review did not definitively support the association of an increased risk of major malformations or cardiac defects association and fluoxetine exposure in the first trimester of pregnancy.

(b) (4)

## Review of Individual Studies included in the meta-analysis

### **1. Einarson A, Choi J, Einarson TR, Koren G. 2009. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry*. 54(4):242-246.**

#### Method

The Canadian Motherisk Program conducted a prospective cohort study to determine if antidepressants increase the risk for major malformations. The Motherisk Program at the Hospital for Sick Children in Toronto is a teratogen information service. Exposure information and follow-up outcomes information were obtained by telephone interview. Outcomes were confirmed with medical records. Women ( $n = 928$ ) met the criteria for inclusion if they were exposed to fluoxetine in the first trimester of pregnancy and gave birth to a live-born infant were matched to women ( $n = 928$ ) in the comparison group. The comparison group included women who had called the Motherisk Program who were exposed to a non-teratogen and not exposed to an antidepressant. The two groups were matched for maternal age, smoking, and alcohol use.

#### Results

There were 30 (3.2%) major malformations in the antidepressant group and 31 (3.3%) in the comparison group (OR 0.9; 95% CI 0.5 to 1.61). Each antidepressant was not analyzed separately, as the study lacked a large enough sample size. The fluoxetine exposure group included 61 exposures, and the following three malformations:

- pulmonary valve stenosis
- hypospadias
- ventricular septal defect.

The authors conclude that as a group, antidepressant use in the first trimester of pregnancy is not associated with an increased risk for major malformation above the baseline. In addition, no individual antidepressant was associated with an increased risk of a specific malformation.

The sponsor rated the quality score of this study 39%.

### Limitations

The authors acknowledged that there may be selection bias as women who call a teratogen information service do not necessarily reflect the general population, because women who participate in this type of research generally have a higher socioeconomic status and are more motivated to improve the outcome of their pregnancy.

### *Reviewer comments*

- *A strength of this study is that outcomes were confirmed by medical records*
- *Limitations of this study include:*
  - *Exposure information, tobacco, alcohol, and illicit drug use were self-reported.*
  - *Definitions of major malformations and cardiovascular malformations are not provided*
  - *Underlying diseases were not controlled for*
  - *The dates of the study are not provided*
- *These limitations and the small sample size preclude the usefulness of this study in evaluating the effect of in-utero fluoxetine exposure.*
- *The sponsor did not include this study in the cardiovascular malformation meta-analysis because there was no statistical analysis for fluoxetine, only for SSRIs overall.*

**2. Diav-Citrin O, Shechtman S, Weinbaum D, Wajnberg R, Avgil M, Di Gianantonio E, Clementi M, Weber-Schoendorfer C, Schaefer C, Ornoy A. 2008. Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study. Br J Clin Pharmacol 66(5):695-705.**

### Method

This is a prospective multicenter cohort study that evaluated the rate of major congenital malformations following first trimester in-utero exposure to fluoxetine (n=346) or paroxetine (n=463) compared to a control group (n=1467). The study enrolled pregnant women who contacted the Israeli Teratology Information Service (TIS) (Jerusalem, Israel) and the Servizio di Informazione Teratologica (Padua, Italy) between 1994 and 2002, and the Pharmakovigilanz-und Beratungszentrum für Embryonaltoxikologie (Berlin, Germany) between 2002 and 2005 in Germany. The three TISes use similar methodologies and are all members of the European Network of Teratology Information Services, an organization that provides counseling services on environmental exposures during pregnancy.

The exposed groups were compared with a control group of women who contacted one of the three participating centers during pregnancy regarding exposures to drugs known to be non-teratogenic in similar time frames. The following information was recorded: maternal demographics, medical and obstetrical histories, exposure details (dose, duration and timing in pregnancy). After the expected date of delivery, follow-up was conducted by telephone interview or mailed questionnaire to the woman or the child's pediatrician to obtain details of the pregnancy outcome, gestational age at delivery, birth weight, congenital anomalies, neonatal complications, and SSRI and other exposure information. This follow-up was performed between the neonatal period and six years of age. However, in most cases it was carried out within the first two years of life.

Major anomalies were defined as structural abnormalities that have serious medical, surgical or cosmetic consequences. The authors stated that ventricular septal defects (VSDs) were considered major anomalies of the heart, because they carry a risk of infectious endocarditis and require prophylactic antibiotics before invasive procedures. Significant neurodevelopmental or functional problems were also considered major anomalies when they required special education or interventions, even in the absence of a structural abnormality.

### Results

When the analysis excluded major malformations associated with chromosomal or genetic disorders, there was an approximately two-fold increase in the overall rate of congenital anomalies in the groups exposed to paroxetine or fluoxetine during the first trimester compared with the control group (see Table 1 below). This increase in risk appeared to be driven by an increase in cardiovascular anomalies. There were no significant differences among the three groups when the noncardiovascular anomalies were compared. The authors did not present ORs.

**Table 1**  
Pregnancy outcome

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The following major cardiovascular anomalies occurred following prenatal fluoxetine exposure:

- Transposition of the great arteries and ventricular septal defect (VSD)
- Small muscular VSD (discovered at 6 months of age, closed by 1 year)
- Pulmonary valve stenosis
- Unspecified congenital heart disease-this patient was also exposed to carbamazepine and clonazepam
- Mild pulmonary artery stenosis- this patient was also exposed to clonazepam
- Atrial septal defect (ASD)
- ASD (needed catheterization)
- Critical aortic valve stenosis with dysplastic bicuspid aortic valve
- VSD (closed)

The adjusted ORs for cardiovascular malformations following first trimester exposure to paroxetine or fluoxetine were 2.66 (95% CI 0.80-8.90) and 4.47 (95% CI 1.31-15.27), respectively. The authors concluded that this study suggests a possible association between cardiovascular anomalies and first-trimester exposure to fluoxetine; however, they comment that these results should be interpreted with caution based on the wide confidence intervals. They also commented that while the diversity in cardiac anomalies argues against a plausible underlying mechanism, the study results can not rule out a causal association. The authors also note that these results could be due to chance and that other studies are needed to verify their findings. The study controlled only for the following potential confounding factors: maternal age, chromosomal anomalies, and smoking.

The sponsor rated the quality score of this study 52%.

#### Study Limitations

Concomitant psychiatric medication was used by 45.7 % of the fluoxetine treated women, and in 31.5%, the combination was with a benzodiazepine. The authors acknowledge that there may be selection bias, because more frequent screening of newborns born to mothers exposed to SSRIs during gestation may result in greater frequency of anomaly detection in this cohort. They also acknowledge that one patient with a cardiovascular malformation in the fluoxetine group was also exposed to carbamazepine, which is associated with cardiovascular malformations. Other limitations of the study include the following: reliance on maternal interview as a source for outcome data in most cases, lack of direct physical examination of the offspring, variation in timing of follow-up, and lack of data on socioeconomic status, and a large loss to follow-up rate in the fluoxetine group (13-56% across different sites).

#### *Reviewer comments:*

*In addition to the limitations discussed by the authors, this study is also limited by the fact that it did not control for the effects of: underlying maternal illness, severity of depression, maternal obesity, and exposure to alcohol. The affected case with concomitant carbamazepine exposure in-utero should not have been included in the statistical analysis, as carbamazepine is a known teratogen. The two cases of VSD that closed spontaneously should have been excluded from the analysis for both exposed and unexposed cohorts as they do not have any clinical significance and therefore should not be reported as major malformations. The case with ASD without any information regarding severity is not useful because it does not provide any information on the*

*clinical significance of the finding. The large loss to follow-up rate also introduces selection bias.*

*Concomitant exposure to fluoxetine and a benzodiazepine may be an important confounder, especially in view of data (see discussion of study 6, Oberlander 2007 below) that show an increased risk of cardiovascular malformations following exposure to a combination of an SSRI and a benzodiazepine. The fact that 45.7% of the fluoxetine group were also exposed to other psychiatric medications raises the issue that perhaps there may be characteristics, other than concomitant medication exposure, particular to this group that increases their teratogenic risk, such as severity of disease and/or concomitant anxiety disorder.*

*This is the only published study in the literature that shows an increased risk of cardiovascular malformations following first trimester fluoxetine exposure. Therefore, these findings need to be corroborated by others. In view of the limitations discussed, it is not possible to draw a conclusion regarding these study findings.*

**3. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. 1996. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 335(14):1010-1015.**

Method

This prospective cohort study identified 163 pregnant women taking fluoxetine during the first trimester of pregnancy between 1989 and 1995 and compared the outcomes of their pregnancies with those of 254 women identified in a similar manner but who did not take fluoxetine. The population studied was women who called the California Teratogen Information Service and Clinical Research Program about exposure to teratogenic and nonteratogenic drugs and/or procedures. The fluoxetine exposure group was compared with pregnant women who called for information about exposure to a non-teratogen. A major anomaly was defined as a structural defect that occurs in less than four percent of the general population and has cosmetic or functional importance. A minor anomaly was defined as a structural defect that has no cosmetic or functional importance and that occurs in less than four percent of the general population.

Each woman enrolled in the study completed a questionnaire that included her history of previous pregnancies and family medical history, socioeconomic and demographic information for her and her partner, and exposures during the current pregnancy. The exposure history included: dosages, dates, and indications for all medications; use of caffeine; use of supplemental vitamins; occupational exposures; infectious or chronic disease; prenatal testing or other medical procedures; and use of recreational drugs, tobacco, and alcohol. Each woman was provided with a diary to record any additional exposures that occurred during the pregnancy. Exposure information was also collected by calling the enrolled women throughout their pregnancies.

Birth outcome was recorded on a standard form completed by telephone interview with each mother shortly after delivery, and medical records were examined after their release. In addition, the infant's physician was asked to return a form reporting the presence or absence of any major

anomaly. When possible, infants were examined by one of the authors for both major and minor anomalies. In 11.5 percent of patients, birth outcomes were reported only by the mother.

### Results

The rate of major congenital structural anomalies was not statistically significantly different between the two groups (5.5% among fluoxetine group versus 4.0% among controls,  $p=0.63$ ). However, the incidence of three or more minor anomalies was significantly higher among the 97 infants exposed to fluoxetine who were evaluated for minor anomalies than among the 153 similarly examined control infants (15.5% versus 6.5%,  $p=0.03$ ). No pattern was recognized for either major congenital or minor malformations.

This study did not include an analysis of cardiovascular malformations; however, the following defects occurred in the fluoxetine group:

- 1 ventricular septal defect
- 1 ventricular septal defect with bilateral cryptorchidism
- 1 atrial septal defect.

There was one VSD in the control group.

The sponsor rated the quality score of this study at 59%.

### Limitations

The authors stated that they could not rule out weak associations in a study of this size.

#### *Reviewer comments*

1. *This study is limited by the small sample size, and self-reporting of exposure information.*
2. *All of the cardiac malformations were confirmed by an examining investigator, and the raw incidence of cardiac malformation among infants exposed to fluoxetine during the first trimester was 1.8% (3 of 164 infants) compared to 0.4% (1 of 226 ) control infants. The authors did not statistically analyze these outcomes due to the small size of the study and its limited power. However, this reviewer notes and presents this difference.*

**4. Pastuszak A, Schick-Boschetto B, Zuber C, Feldkamp M, Pinelli M, Sihn S, Donnenfeld A, McCormack M, Leen-Mitchell M, Woodland C, et al. 1993. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). JAMA 269(17):2246-2248.**

### Method

This prospective cohort study compared pregnancy outcomes of 128 women with first trimester exposure to fluoxetine with a control group of 128 women exposed to nonteratogens, and 74 women exposed to tricyclic antidepressants (TCAs). This study enrolled pregnant women who contacted one of four Teratogen Information Services (TIS) requesting counseling about the teratogenic potential of fluoxetine. The participating centers were Motherisk (Toronto, Ontario), Pregnancy Healthline (Philadelphia, Pa), Pregnancy Risk Information Service (Camden, NJ), and Pregnancy RiskLine (Salt Lake City, Utah).

Prospective collection of information and follow-up data were consistent between centers, although they were collected in different manners. Motherisk referred all women concerned about first-trimester fluoxetine exposure to a weekly clinic during which information regarding indication, dose, toxicity, and dates of initiation and discontinuation was obtained in an interview with a team physician. Obstetric, medical, genetic, and drug exposure history was obtained from both the mother and biological father of the fetus. Approximately 8 to 12 months after the expected date of delivery, all patients were contacted by telephone and asked details about the outcome of pregnancy, birth weight, presence or absence of birth defects, and perinatal and neonatal complications. All follow-up information was corroborated by written documentation from the child's physician.

Pregnancy Healthline (Philadelphia), Pregnancy Risk Information Service (Camden), and Pregnancy RiskLine (Salt Lake City) recorded similar maternal information by telephone interviews. Postnatal follow-up data, similar to those collected by Motherisk in Toronto, were obtained by telephone (Philadelphia, Salt Lake City, and Camden) or follow-up cards received in the mail (Philadelphia). Each woman exposed to fluoxetine during the first trimester was age-matched (+/- 2 years) to two controls, closest in date to the date of consultation of the fluoxetine case. The first control group consisted of pregnant women who sought counseling at Motherisk after first-trimester exposure to tricyclic antidepressants (TCAs) for their depression, and the second control group consisted of pregnant women who sought counseling at Motherisk regarding exposure to a nonteratogen, the nonteratogenic controls (NTCs). A nonteratogen was defined as a medication or environmental agent that, in large studies, has been shown not to increase teratogenic risk (eg, acetaminophen, penicillins, dental x-rays). Both control groups were selected from the Motherisk computerized database.

### Results

The reported data are divided into comparisons between 128 fluoxetine cases and 128 age-matched NTCs, and comparisons among 74 TCA cases, 74 age-matched fluoxetine cases, and 74 age-matched NTCs. Babies born to women exposed to fluoxetine during the first trimester of pregnancy did not have a statistically increased risk for major congenital malformations compared with babies born to women in the NTC group (2% in the fluoxetine group vs. 1.8 % in the NTC group,  $p=0.3$ ). This remained true when the smaller fluoxetine sub-cohort ( $N = 74$ ) was compared with both of its controls (3.4% vs. 0% (TCA) vs. 3% (NTC),  $p=0.8$ ).

The authors did not discuss the rate of cardiovascular malformations; however, cardiovascular malformations were listed under the major malformation category. One VSD and one jejunal obstruction occurred in the fluoxetine group. One VSD and one case of pulmonary atresia occurred in the NTC group, and there were no major malformations in the TCA group.

The sponsor rated the quality score of this study 50%.

### Limitations

The authors stated that this study had limited power to rule out minimal increases in risk above baseline due to the small sample size ( $n=128$ ).

### *Reviewer comments*

1. *This is a descriptive study only with no statistical analysis, and the authors were unable to control for potential confounders.*
2. *The raw incidence of cardiac malformation among infants exposed to fluoxetine during the first trimester was 1.0% (1 of 98 infants) compared to 0% in the tricyclic exposed control group, and 1.8% (2 of 110 ) in the nonteratogen control group. The authors did not statistically analyze these outcomes due to the small size of the study and its limited power. However, this reviewer notes and presents this information.*

**5. Oberlander TF, Warburton W, Misri S, Riggs W, Aghajanian J, Hertzman C. 2008. Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. Birth Defects Res B Dev Reprod Toxicol 83(1):68-76.**

Method

This is a retrospective cohort study that used medical record and prescription data to determine a population-based incidence of congenital anomalies following prenatal exposure to SSRI antidepressants used alone and in combination with a benzodiazepine (BZ).

Data used in this study came from the British Columbia (BC), Canada Linked Health Database (administrative data sources from the BC registry of births, hospital separation records, the PharmaCare registry of subsidized prescriptions, the Medical Services Plan physician billing records and the registry of Medical Services Plan subscribers) linked to PharmaNet, a province-wide network recording all prescriptions dispensed by BC pharmacists outside hospitals. These data were processed by the Centre for Health Services and Policy Research (CHSPR), UBC; PharmaNet provided records with the same unique, non-identifying study ID as was provided by CHSPR to enable data linkage. The cohorts used in this study were assembled from records of 203,520 registered live births (hospital and home births) in British Columbia that occurred between April 1, 1997 and March 31, 2002. Exposure groups were defined as SSRI monotherapy and SSRI+benzodiazepines (BZ) used in combination. The study compared outcomes of infants exposed to SSRI monotherapy or SSRI+BZ combination with infants who had no exposure to either of these drugs in the first trimester, respectively. Outcomes were identified using ICD9 codes for major congenital anomalies (codes: 740.0 to 759.9), and the subset of cardiovascular defects (745.0–747.9).

To control for maternal illnesses that may have also contributed to congenital anomalies, physician billing data were used to determine whether the mothers had diseases and complications related to pregnancy (ICD9 codes from 640 to 648, Complications Mainly Related to Pregnancy). In addition, any diagnosis of epilepsy or seizures was also identified from maternal records regardless of timing of exposure, as these were excluded from the study in order to avoid any confounding effect. The study analysis controlled for maternal exposures to methadone, antipsychotics and clonazepam or clobazam.

Results

Rather than reporting the results as odds ratios, the authors used risks and risk differences (RDs; 95% confidence intervals). (Therefore, a statistically significant risk difference has a confidence interval that does not cross zero.)

The data did not show an increased risk for major congenital anomalies or cardiovascular anomalies among women who received monotherapy with fluoxetine (n=638). Exposure to fluoxetine and a benzodiazepine (n=81) was associated with an increased risk for major congenital anomalies, after controlling for potential confounders (RD 5.18; 95% CI 0.3-10.07). Exposure to fluoxetine and a BZ was associated with an increased risk for cardiovascular malformations; however, after controlling for confounders, this increase was not statistically significant (RD 1.94; 95% CI -0.3-4.19).

The sponsor rated the quality score for this study 70%.

### Limitations

The authors stated that their findings were limited by the small number of cases (fluoxetine and BZ group n=7 major malformations, fluoxetine and BZ group n=2 cardiovascular malformations). While the authors' analysis accounted for some confounding factors, data on other potential confounders (such as maternal obesity, use of tobacco, alcohol, and illicit drugs) were not available.

### *Reviewer comments*

- 1. Exposure to drug was not confirmed.*
- 2. Outcomes are not always accurately coded in claims databases, and therefore, there may be some degree of incorrect reporting of outcomes in this dataset.*
- 3. Although the increased risk for cardiovascular malformations following combination fluoxetine and BZ exposure did not reach statistical significance, there was a statistically significant increased risk for major malformations following exposure to an SSRI and BZ (RD 1.18; 95% CI 0.18-2.18). We should therefore take this trend into consideration as a potential risk factor when evaluating data from other studies.*

## **6. Malm H, Klaukka T, Neuvonen PJ. 2005. Risks associated with selective serotonin reuptake inhibitors in pregnancy. *Obstet Gynecol* 106(6):1289-1296.**

### Method

The primary objective of this retrospective cohort study was to study whether exposure to SSRIs during early pregnancy is associated with an increased risk of major malformation. The secondary objective was to study the effect of continuous exposure to drug on the length of gestation and birth weight. Data were derived from four linked Finnish registers from 1996-2001: The Medical Birth Register, The National Register of Congenital Malformations, The National Register on Induced Abortions, and The Drug Reimbursement Register.

The Medical Birth Register collects maternal background data, maternal pregnancy-related medical data, delivery data (live births and stillbirths), and neonatal outcomes data until seven days of age, including malformations. It includes information on length of gestation at delivery based on last menstrual period and ultrasound examination. All infants born in hospitals are examined by a pediatrician before discharge. All births of infants or fetuses with a gestational age of at least 22 weeks or birth weight of 500 g or more are included in the register. The National Register of Congenital Malformations defines a major congenital anomaly as a significant congenital structural anomaly, chromosomal defect, or congenital hypothyroidism. The registry collects information on all newborns with a birth defect, using several data sources. Delivery units are obliged to complete and forward a special data collection form on malformations to the Malformation Register. The Drug Reimbursement Register contains data on all reimbursed prescription drug purchases for all permanent Finnish residents. It also includes data on chronic illnesses requiring continuous drug treatment. Medicines are dispensed in three month supplies.

The study defined cases as women with singleton pregnancies who made at least one purchase of an SSRI drug during the time period from one month before conception and the day pregnancy ended ( $n = 2,077$ ). Women with chronic illnesses that required continuous medication were excluded from the analysis ( $n = 273$ ). Twenty-two cases were excluded because their matched control had a chronic illness. The analysis included 1,782 cases and 1,782 controls. The control group was defined as women with no reimbursed drug purchases during the defined exposure period. Initially, controls were matched with cases by the year pregnancy ended, age, parity, geographic area, and social status. Then one control was randomly selected from the case-specific matched control pool for each case. The study analysis considered the following variables: major malformations, low Apgar score, treatment in a special or intensive care unit, low birth weight, small for gestational age, purchase of SSRIs, low social status, smoking, artificial reproductive techniques, previous deliveries, maternal age, and other purchased medications.

There were 525 women who purchased fluoxetine in the first trimester out of a total number of 1,398 first trimester SSRI purchases (first trimester defined as 1 month before conception to 12 gestational weeks).

## Results

Malformation rates did not differ between women who purchased any SSRI in the first trimester of pregnancy and their matched controls. The crude reporting rate was higher in the fluoxetine group compared with that in the comparison group. Pregnancies with fluoxetine purchases during the first trimester had 29 (5.5%) malformations (including 12 cases of isolated cardiovascular anomalies) compared with 62 (3.5%) in the control cohort ( $p=0.03$ ). After excluding chromosomal abnormalities, fluoxetine purchasing women had 25 (4.8%) malformations compared with 52 (2.9%) in the control cohort ( $p=0.04$ ). However, no statistically significant association was observed between fluoxetine exposure and the risk of major malformation after controlling for the effects of maternal age, smoking, low social status, nulliparity, and purchases of other reimbursed drugs other than SSRIs during the corresponding period. The adjusted OR was 1.7 (95% CI: 0.9 to 3.3).

The authors stated that the prevalence of cardiac malformations following fluoxetine exposure was nearly three times that of the Finnish population. Eight of the 12 cardiovascular malformations were isolated cases of ventricular septal defects; however, the authors did not present any data on the severity of these cases. The authors commented that these isolated VSDs often close spontaneously.

The sponsor rated the quality score for this study 81%.

### Limitations

There were no data on potential confounders such as maternal obesity and use of alcohol and illicit drugs, and drug exposure and timing of exposure were not confirmed. No adjustment was made for multiple comparisons.

### *Reviewer comments*

- 1. The authors do not present descriptions of the 12 cardiovascular malformations, the number of cardiovascular malformations in the control group, or a statistical analysis. In a personal communication with the author on May 5, 2010, she stated that they did not compare the number of cardiovascular malformations in the fluoxetine group with the control group. All of these limitations make it difficult to draw any conclusions regarding the cardiovascular malformations.*
- 2. The sponsor did not include this study in the cardio-vascular meta-analysis because of the lack of data on the specific cardiovascular malformations.*

### **Case-control Studies Included in the Sponsor's Post-hoc Analysis**

- 7. Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM; National Birth Defects Prevention Study 2007. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 356(26):2684-2692.**

### Method

The authors conducted a case-control study using the National Birth Defects Prevention Study to evaluate the relationship between maternal SSRI use in the first trimester and the occurrence of selected birth defects. Case infants experiencing birth defects (N=9,622) born between October 1, 1997 and December 31, 2002, were identified through birth-defects surveillance systems from eight states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas). Control infants (N=4,092), those who did not experience birth defects, were selected randomly from the same geographic areas as the case infants.

Information on exposure to SSRIs, other potential risk factors, and demographic information were collected by standardized telephone interviews with mothers of case and control infants from 6 weeks to 2 years after the estimated date of delivery. Interviews were conducted in English or Spanish. Exposure to SSRIs was defined as treatment with any SSRI from one month before to three months after conception. Women who took non-SSRI antidepressants were included in the unexposed group. Information on the infants in each defect category was

reviewed by clinical geneticists who were unaware of the infants' exposure status and confirmed case eligibility. Each case of cardiac birth defect was reviewed by a team of experts in pediatric cardiology and the epidemiology of heart defects, and was assigned to a single cardiac diagnostic category. The study excluded infants with chromosomal anomalies and single-gene disorders. Due to the strong association between diabetes and birth defects, infants of mothers with pre-pregnancy type 1 or 2 diabetes were excluded from the study.

### Results

Seventy-six infants with designated major malformations (cases) were exposed to fluoxetine, and 29 infants without major malformations were exposed to fluoxetine. The study did not find a statistically significant difference in likelihood of fluoxetine exposure between case and control infants for all major birth defects combined (adjusted OR 1.1, 95% CI 0.7-1.7), cardiac birth defects (adjusted OR 1.2, 95% CI 0.7-2.1), non-cardiac birth defects, or the group of anencephaly, craniosynostosis, and omphalocele. There were 432 craniosynostosis cases in the study; among them, 10 were exposed to fluoxetine. The adjusted OR for craniosynostosis was 2.8 (95% CI: 1.3 to 6.1), after controlling for maternal race or ethnic group, maternal obesity, maternal smoking, and family income. None of the mothers of case infants associated with SSRI use were concomitantly exposed to medications with a known teratogenic effect.

The sponsor rated the quality score for this study 78%.

### Limitations

The authors acknowledged the small number of exposed infants for each individual defect as a limitation to their study. They also acknowledged that the large number of comparisons evaluated during their analysis could have resulted in chance associations, and that the severity of the underlying depression was not controlled for. Dosing data were not available, so dose-response relationships could not be assessed.

### *Reviewer comments*

- 1. Obtaining exposure information through retrospective telephone interview may result in recall bias.*
- 2. The finding of an association between in utero fluoxetine exposure and craniosynostosis in the infant has not been corroborated by other investigators.*

**8. Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA 2007. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med 356(26):2675-2683.**

### Method

The authors conducted a case-control study using the Slone Epidemiology Center Birth Defects Study to look for potential associations between first-trimester maternal use of SSRIs and the risk of birth defects among case infants (N=9,849) and control infants (N=5,860). Case infants with malformations were identified from five study centers in the United States (areas surrounding Boston, Philadelphia, and San Diego, and a portion of New York state) and Canada

(suburban Toronto). Control infants were enrolled from study hospitals and a population-based random sample of newborns in Massachusetts. This study included women whose last menstrual period occurred between January 1, 1993 and December 31, 2004.

Outcomes that were evaluated included craniosynostosis, omphalocele, and heart defects. Because heart defects represent developmentally diverse outcomes, the authors divided the defects into seven developmentally based subgroups. They also evaluated other specific defects that occurred in at least 100 enrolled subjects overall and at least five exposed subjects. A clinical geneticist with training in pediatric cardiology reviewed the diagnostic codes (ICD-9) for each case and assigned each case to one or more of these seven cardiac defect subgroups whenever possible. When two defects coexisted, the category assignment was developmentally based.

The study used 45-to-60-minute interviews of mothers (in person until 1998 and by telephone thereafter) within 6 months of delivery to obtain drug exposure information and other information on demographic, reproductive, and medical factors, cigarette smoking, and the consumption of alcohol and caffeine. The interviews were conducted by trained study nurses who were unaware of the study hypotheses. Detailed data were collected on all medications (prescription, over-the-counter, vitamins and minerals, and herbal products) used at any time from 2 months before conception through the end of the pregnancy.

Exposure to SSRIs was defined as any SSRI use from 28 days before the last menstrual period through 112 days after the last menstrual period (LMP). The reference group for all analyses was women not exposed to any antidepressant at any time from 56 days before LMP through the end of pregnancy. The study excluded subjects whose infants had chromosomal abnormalities, known Mendelian inherited disorders, syndromes, birth defects of known cause (e.g. fetal alcohol syndrome), and metabolic disorders. The analysis of specific SSRIs excluded women who took more than one SSRI.

## Results

The study did not find a statistically significant increased risk of major malformation, cardiac defects overall, or specific cardiac defects associated with use of fluoxetine. Among the fluoxetine-exposed group, there were 31 (0.8%) cardiac defects with an adjusted odds ratio of 0.9 (95% CI: 0.6 to 1.5) after controlling for: maternal age, maternal race or ethnic group, maternal education, year of last menstrual period, study center, first-trimester smoking status, first trimester alcohol consumption, history of birth defect in first-degree relative, pre-pregnancy BMI, parity, presence or absence of seizures, diabetes mellitus, hypertension, infertility, and first-trimester use of folic acid. There was no fluoxetine exposure among craniosynostosis or omphalocele cases.

Analyses of the associations between individual SSRIs and specific defects showed significant associations between sertraline and omphalocele (n=3; OR 5.7; 95% CI, 1.6 to 20.7) and septal defects (n=13; OR 2.0; 95% CI, 1.2 to 4.0) and between the use of paroxetine and right ventricular outflow tract obstruction defects (n=6; OR 3.3; 95% CI, 1.3 to 8.8).

The sponsor rated the quality score for this study 76%.

### Limitations

The authors acknowledged that the study did not adjust for multiple comparisons, and therefore, any association could be due to chance.

### *Reviewer comments*

1. *Obtaining medical and exposure information through retrospective telephone interview can result in recall bias.*
2. *The study did not control for the effects from underlying maternal depression.*
3. *This study excluded women exposed to more than one SSRI.*

### **Studies Published after the Sponsor's Meta-analysis cut-off date**

- 9. Pederson L, Henriksen T, Vestergaard M, Olsen J, Bech B. 2009 Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 23(339): b3569 doi:10.1136/bmj.b3569.**

### Method

This prospective cohort study was based on data from the Danish Registry and included 496,881 singleton liveborn children between January 1, 1996 and December 31, 2003 in the final study population. The investigators used data from four Danish nationwide registries: the medical birth registry, the national register of medicinal product statistics, the fertility database, and the national hospital register. The registries were linked through the use of the unique personal identifier of 10 digits assigned to all citizens at birth.

The authors defined exposure as filling two or more prescriptions 28 days before to 112 days after the beginning of gestation. The study excluded women who filled a prescription for insulin or antihypertensive medications during the three months before the estimated date of conception. Women who filled a prescription during the exposure window for a non-SSRI antidepressant or for other psychotropic medications (such as antiepileptics, antipsychotics, and/or anxiolytics) were excluded from the main analyses but included in later sensitivity analysis. A total of 1,370 mothers were exposed to an SSRI, of which 348 mothers were exposed to fluoxetine.

Malformations were coded according to the Eurocat categorization, and congenital heart defects were further categorized using developmentally based subgroups as suggested by Louik et al. Only live born children were included in the analyses, as information on malformations in stillbirths is incompletely registered. Only malformations detected at birth or within the first year after birth were included. The authors also performed additional analyses after two years to investigate for potential differences in time of diagnosis.

### Results

First trimester exposure to fluoxetine was not significantly associated with either an increased risk for major malformation overall (OR 1.00, 95% CI: 0.53-1.88), or for cardiac malformations

(OR 0.77, 95% CI 0.19-3.11), after adjusting for maternal age, calendar year, income, marriage status and smoking.

Filling a prescription for more than one type of SSRI was associated with septal heart defects (adjusted OR 4.70, 95% CI 1.74-12.7). This may represent a change in SSRI or simultaneous use of different SSRIS. The authors did not present data for various combinations of SSRIs.

Follow-up on congenital malformations in the children for two years after birth resulted in similar results to the one year follow-up.

### Limitations

Because pharmacy records are limited only to dispensing of medication, actual exposure could not be confirmed. Malformations were coded according to the Eurocat categorization, but it is not clear whether the cases were medically confirmed or just based on diagnostic codes. There was no information on the severity of maternal depression, and the analysis did not control for underlying maternal disease. As the authors pointed out, all potential confounders were considered in crude categories, thus residual confounding or unmeasured confounding might still be present. The authors also acknowledged that no adjustments were made for multiple comparisons.

### *Reviewer comments*

*Although there was an increased risk for septal heart defects in women who filled a prescription for more than one type of SSRI, it is not clear whether this occurred in women who used them simultaneously, or who discontinued one SSRI, and started a different one. It also raises the question of whether the severity of depression or other exposures such as alcohol, and illicit drug use played a factor.*

**10. Merlob P, Birk E, Sirota L, Linder N, Berant M, Stahl B, Klinger G. 2009. Are selective serotonin reuptake inhibitors cardiac teratogens? Echocardiographic screening of newborns with persistent heart murmur. Birth Defects Res A Clin Mol Teratol 85(10):837-841.**

### Methods

The authors conducted a prospective cohort study to compare the rates of congenital heart malformations in SSRI-exposed versus non-exposed newborns during the first trimester in Rabin Medical Center and Schneider Children's Medical Center of Israel from 2000 to 2007. All newborns delivered during the study period who had a persistent cardiac murmur on the second or third day of life were referred for examination by a pediatric cardiologist and by echocardiography. The diagnostic findings were compared between the newborns who were exposed to SSRIs and those who were not.

During the last two years of the study, the cardiologists were not blinded to SSRI exposure due to increased awareness of the possible association between prenatal SSRI use and cardiovascular malformations in the offspring. Any infant with multiple congenital anomalies or dysmorphic features underwent genetic evaluation by a trained expert to exclude a congenital syndrome.

Newborns with chromosomal defects, syndromic heart malformations, functional murmurs, isolated persistent foramen ovale, isolated peripheral pulmonic stenosis, and isolated patent ductus arteriosus were excluded.

The study was based on data collected prospectively by the Departments of Neonatology in Rabin Medical Center and Schneider Children's Medical Center of Israel as part of a continuous surveillance programs affiliated with the European Network Teratology Information Services and with the International Clearinghouse for Birth Defects Surveillance and Research. A standardized pregnancy questionnaire was administered to all women on admission to the maternity ward and reviewed by the attending neonatologist. The questionnaire obtained the following information: use of any drug during pregnancy, maternal diseases, smoking, alcohol consumption, and irradiation. Following hospital discharge, all charts are reviewed and information regarding congenital birth defects and drug use was collected.

### Results

Among 67,871 infants born during the study period, nonsyndromic congenital heart defects (all cases were mild) were identified by echocardiography in 8 of 235 (3.40%) newborns exposed in utero to any SSRI and 2 of 66 (3.03%) newborns exposed to fluoxetine. There were 1083 nonsyndromic congenital heart defects among 67,636 (1.60%) non-exposed newborns. The study analysis suggested an increased risk of mild congenital heart defects (RR 2.17; 95% CI: 1.07-4.39) associated with first-trimester SSRI exposure. The authors did not calculate a risk ratio for the cardiovascular malformations in the first-trimester fluoxetine exposure, probably due to the small sample size (n=2/66). The two cardiovascular malformations in the fluoxetine group were mild VSDs.

### Limitations

The authors acknowledged the small sample size as the main limitation of the study. Other limitations included the lack of information on some potential confounders such as race and maternal obesity.

### Reviewer comments

- 1. The sponsor used the raw counts of cardiac heart defects in the fluoxetine and non-fluoxetine groups, to calculate an unadjusted risk ratio of 1.89 (0.48-7.42). This does not suggest a statistically significantly increased risk.*
- 2. The very limited sample size in the fluoxetine group makes it difficult to draw any conclusions regarding the authors' findings and the sponsor's calculated risk ratio.*
- 3. The loss of cardiologist blinding to SSRI exposure in the last two years of the study may have introduced detection bias.*

### **Review of Other Studies Not Used For the Post-Hoc Analysis**

**11. Kallen BA, Otterblad P. 2007. Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. Birth Defects Res A Clin Mol Teratol 79(4):301-308.**

Methods

This retrospective cohort study utilized three linked Swedish health registers to investigate whether use of SSRIs during the first trimester of pregnancy is associated with an increased risk of congenital malformations in exposed infants. This study was based on three Swedish health registers: the Medical Birth Register, the Register of Congenital Malformations, and the Hospital Discharge Register. The sponsor did not include this study in the meta-analysis, because the outcome definitions in this study are different from the outcome definitions of the meta-analysis and other studies, and there was no control group. In this study, the outcome “malformation” included “minor conditions of little clinical significance” while the meta-analysis and other studies used only major malformations as the primary outcome measure. The definition of “cardiac malformation” was not specified in this study.

The following data from these registers were used in the study:

- Year of birth: enrollment was limited to births that occurred between July 1, 1995 and December 31, 2004.
- Maternal age in 5-year groups (<20, 20-24, 25-29, etc.)
- Parity (1, 2, 3, and  $\geq 4$ )
- Number of previous miscarriages (none, 1, 2, and  $\geq 3$ )
- Maternal smoking early in pregnancy (none, < 10 cigarettes/day,  $\geq 10$  cigarettes/day)
- Maternal pre-pregnancy weight and height (BMI was calculated)
- Couple subfertility by years of unwanted childlessness (none, 1, 2, 3, 4, or  $\geq 5$ )
- Maternal use of drugs in early pregnancy and up to the first antenatal visit. Information included drug names, dosage, and time of use, but sometimes the information was incomplete.

Results

In this study, 6,481 mothers of 6,555 infants (includes 75 twin pairs) reported the use of any SSRI in early pregnancy (first trimester) during the study period. The fluoxetine group included 919 women (926 infants) who used fluoxetine either alone or with another antidepressant. In this cohort, 860 women only used fluoxetine. Among babies born to women in the fluoxetine-exposed group, there were 36/926 (3.9%) malformations with an adjusted OR of 0.85 (95% CI, 0.61 to 1.19) after controlling for year of birth, maternal age, parity, smoking and  $\geq 3$  previous miscarriages. There was no statistically significant association between fluoxetine (includes fluoxetine use alone and with other antidepressants) and any cardiac malformation (adjusted OR 1.09; 95% CI: 0.62-1.92). There was a significantly increased risk only with use of paroxetine early in pregnancy (OR=1.63, 95% CI 1.05-2.53).

Limitations

The authors commented that information on dose and timing of exposure are often incomplete. With regard to the outcomes, it is not clear whether the outcomes were medically confirmed or

based on ICD diagnoses codes. Also, underlying maternal diseases were not controlled for in the analyses.

The authors commented that one of the strengths of this study is that recall bias was not an issue, because exposure information was collected prior to knowledge of the outcome.

## 12. United Health Care Study (GlaxoSmithKline data)

The i3 or United Health Care study was a retrospective cohort study of major malformations with a focus on cardiovascular defects. It used data in the i3 Drug Safety database from the Ingenix Research Data Mart, a U.S.-based insurance claims dataset, between January 1995 and September 2004. United Healthcare database results compared relatively large groups of patients who were treated with different antidepressants. This data were not included in the meta-analysis as the comparison group included patients taking antidepressants, which is different from the studies included in the meta- analysis.

When these data were published<sup>8,9</sup>, they did not include specific information about fluoxetine exposure and the risks for major malformations or cardiovascular defects. However, fluoxetine-specific data and the final study report are available online from GlaxoSmithKline<sup>10</sup>. Compared to women exposed to other antidepressants, the adjusted odds ratio for major malformations among women (n=1118) exposed to only fluoxetine and nonteratogenic drugs during the first trimester was 0.87 (95% CI: 0.55 - 1.38). The authors also calculated that women exposed only to fluoxetine had an adjusted odds ratio for cardiovascular malformations of 1.26 (95% CI: 0.70 - 2.28) compared to women exposed to other antidepressants. This analysis excluded women exposed to teratogenic drugs affecting the cardiovascular system.

### *Reviewer comments*

- 1. A limitation of this study is that exposures were based on claims.*
- 2. A strength of the study is the use of medical record abstraction to verify outcomes.*
- 3. Although the sponsor stated that they did not include this study in their meta-analysis due to a comparator group involving women who were exposed to an antidepressant, it is not clear why these results were not included in the sponsor's post-hoc analyses, as this is a large sample size with valuable data.*

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<sup>8</sup> Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. 2007. Bupropion in pregnancy and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf* 16(5):474-484.

<sup>9</sup> Cole JA, Ephross SA, Cosmatos IS, Walker AM. 2007a. Paroxetine in the first trimester and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf*. 16(10):1075-85.

<sup>10</sup> GSK Medicine. Final report on bupropion and other antidepressants, including paroxetine, in pregnancy and the occurrence of cardiovascular and major congenital malformations. GSK Medicine web site. Available at: <http://www.gskclinicalstudyregister.com/files/pdf/3494.pdf>.

## DISCUSSION AND CONCLUSIONS

Most human data studies fail to demonstrate an increased risk of major malformations in offspring born to women exposed to fluoxetine during the first trimester of pregnancy. Only the Alwan study showed an increased risk of craniosynostosis, and this finding has not been corroborated by other investigators. While the Diav-Citrin study showed an increased risk of cardiovascular malformations associated with fluoxetine exposure during the first trimester of pregnancy, these findings have not been corroborated by others. In this study, 31.5% of the fluoxetine treated women also were exposed to a benzodiazepine. This may be an important confounder, especially in view of other published data that show an increased risk of cardiovascular malformations following exposure to a combination of an SSRI and a benzodiazepine (Oberlander), or two SSRIs (Pederson). Although the Malm study reported a prevalence of cardiovascular malformations three times higher than the background rate in the Finnish population, the study findings cannot be evaluated as the authors did not present or statistically analyze the data.

Each of the individual studies presented in this review has limitations such as: insufficient power to rule out small increases in risk, inability to confirm drug exposure, issues with confirmation or classification of outcomes, and/or limited adjustments (or lack of adjustments) for potential confounding factors. Information on dose and duration of fluoxetine exposure were usually not available. In addition, some studies may be subject to reporting bias, as newborns of women exposed to SSRIs tend to get more screening.

It is difficult to compare results across studies due to differences in design, methodology, and outcome definitions. For example, some authors considered VSDs and ASDs to be major malformations, while others did not, given that these defects often spontaneously close on their own and ultimately have no clinical significance. Also, outcome assessment occurred at different times, and ranged from the neonatal period to up to six years of age. Extending the duration of outcome assessment may increase the detection of malformations. The studies are also difficult to compare due to differences in adjustments for confounding factors such as severity of maternal depression, concomitant medications, exposure to tobacco, alcohol, and illicit drugs, and other maternal illnesses such as diabetes and maternal obesity, which are associated with an increased risk for cardiovascular malformations. The issue of severity of depression is an important confounder because there may be maternal characteristics particular to this group that increase teratogenic risk. It is not clear whether or not these disease-specific characteristics are related to: concomitant exposure to other SSRIs and/or other psychiatric medication (as suggested by Oberlander and Pederson); the extent of tobacco, alcohol and illicit drug use; and/or physiologic/metabolic/organic changes. These issues require further investigation through future research. This data gap was also noted in a joint report published by the American College of Obstetrician Gynecologists (ACOG) and the American Psychiatric Association (APA) that discusses the possibility that presumed associations between antidepressants and malformations may be complicated by poly-drug interactions or health habits<sup>11</sup>.

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<sup>11</sup> Yonkers Kimberly, Wisner Katherine, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists *Obstetrics and Gynecology* 2009;114 (3) 703-713.

Taking into account all available data sources, their limitations, and analyses to date, it is not possible to draw definitive conclusions about a causal relationship between maternal use of fluoxetine in the first trimester of pregnancy and major malformations overall or cardiovascular defects in the offspring. The isolated findings in individual studies may represent a true detection of increased risk or may be due to chance or failure to adjust for multiple comparisons; however, if there is an increased risk of a cardiovascular or non-cardiac major malformation with first trimester fluoxetine exposure, the risk is likely small.

In view of the OSE DEPI reviewers' conclusion that the meta-analysis conducted by the sponsor is not valid due to unadjusted confounding [REDACTED] (b) (4)

[REDACTED] However, it may be prudent to generally discuss outcomes from the epidemiological studies presented in this review with regard to the risk of congenital malformations overall and/or cardiovascular malformations following fluoxetine exposure in early pregnancy. Overall, these studies have not shown an increased risk of major malformation overall, but one prospective cohort study suggests a possible increased risk for cardiovascular defects in infants of women exposed to fluoxetine during the first trimester of pregnancy compared to infants of women who were not exposed to fluoxetine.

## RECOMMENDATIONS

1. Do not accept sponsor's proposed Pregnancy labeling change as stated in their CBE.
2. Revise the sponsor's proposed labeling to reflect available human data outcomes based on individual study outcomes [REDACTED] (b) (4)
3. The MHT suggests the following revisions to the sponsor's submitted Pregnancy labeling (Appendix A includes the labeling with documented insertions and deletions).

[REDACTED] (b) (4)

**APPENDIX A:**  
**MHT recommended revisions to sponsor's labeling for Pregnancy**

(b) (4)



**Appendix B: Tabular Summary of Population Based Studies on Fluoxetine Exposure During the First Trimester of Pregnancy**

<b>Study</b>	<b>Quality Rating</b>	<b>Outcome Definition</b>	<b>Fluoxetine Sample Size</b>	<b>Study Results</b>	<b>Limitations</b>
<p><b>Study 1</b> Einarson 2009 Prospective cohort study</p> <p>Teratogen Information Service Canada</p>	39%	Not defined	61	<p>Results for SSRIs overall (fluoxetine not analyzed separately)</p> <p>Major malformations: OR 0.9 (95% CI 0.5-1.61)</p> <p>No statistical analysis of cardiovascular malformations</p>	<p>Small sample size</p> <p>Underlying diseases not controlled for</p> <p>Drug exposure and potential risk factors self-reported</p>
<p><b>Study 2</b> Diav-Citrin 2009 Prospective cohort study</p> <p>Teratogen Information Service Israel, Italy, Germany</p>	52%	<p>Structural abnormalities that have serious medical, surgical, or cosmetic consequences</p> <p>Includes VSDs, and ASDs</p>	253	<p>Major malformations rate was 2 times the rate of the control group (OR not provided)</p> <p>Increased risk for cardiovascular malformations: adjusted OR 4.47 (95% CI 1.31-15.27)</p>	<p>Concomitant psychiatric medication use by 45.7% of the fluoxetine treated women (in 31.5% the combination was with a benzodiazepine)</p> <p>Large loss to follow-up rate in fluoxetine group (13 to 56% across sites)</p> <p>Outcomes reported by mother in most cases</p> <p>Underlying diseases, alcohol use, and socio-economic status not controlled for</p>
<p><b>Study 3</b> Chambers 1996 Prospective cohort study</p> <p>Teratogenic information U. S.A.</p>	59%	A structural defect that has cosmetic or functional importance and occurs in less than 4% of the general population.	164	<p>Major malformation rate was not statistically different between the fluoxetine group (5.5%) and the control group (4%)</p> <p>Cardiovascular malformations were not analyzed but occurred at the following rates: 3/164 fluoxetine group 1/226 control group</p>	<p>Small sample size</p> <p>Potential confounders were not controlled for</p> <p>Descriptive analysis only</p>

**Appendix B: Tabular Summary of Population Based Studies on Fluoxetine Exposure During the First Trimester of Pregnancy**

<b>Study</b>	<b>Quality Rating</b>	<b>Outcome Definition</b>	<b>Fluoxetine Sample Size</b>	<b>Study Results</b>	<b>Limitations</b>
<p><b>Study 4</b> Pastuszak 1993 Prospective cohort study</p> <p>Teratogenic information service Canada and U.S.A.</p>	50%	Not defined	98	<p>No increased rate of major malformations</p> <p>Cardiovascular malformations (raw numbers, not analyzed): 1/98 fluoxetine group 2/110 control group (nonteratogen exposure) 0/74 TCA group</p>	<p>Small sample size</p> <p>Potential confounders were not controlled for</p> <p>Descriptive analysis only</p>
<p><b>Study 5</b> Oberlander 2008 Retrospective cohort study</p> <p>Health administrative data sources Canada</p>	70%	<p>ICD9 codes 740.0-759.9 for major malformations</p> <p>ICD9 codes 745.0-747.9 for cardiovascular malformations (includes VSDs and ASDs)</p>	<p>638 monotherapy with fluoxetine</p> <p>81 exposure to fluoxetine and a benzodiazepine</p>	<p>No increased rate of major malformations or cardiovascular malformations with fluoxetine monotherapy</p> <p>Fluoxetine and a benzodiazepine showed an increased risk for major malformations: Adjusted RD 5.18( 95% CI 0.3-10.07) - risk for cardiovascular malformations was not statistically significant</p>	<p>Small sample size in the fluoxetine-benzodiazepine group</p> <p>No adjustments for potential confounders such as maternal obesity, alcohol use, tobacco, and illicit drug use were not controlled for</p> <p>Claims databases do not always accurately capture outcomes</p> <p>Exposures were not confirmed</p>

**Appendix B: Tabular Summary of Population Based Studies on Fluoxetine Exposure During the First Trimester of Pregnancy**

<b>Study</b>	<b>Quality Rating</b>	<b>Outcome Definition</b>	<b>Fluoxetine Sample Size</b>	<b>Study Results</b>	<b>Limitations</b>
<p><b>Study 6</b> Malm 2005 Retrospective cohort study</p> <p>Four population-based healthcare registries Finland</p>	81%	Major malformation: a significant structural anomaly, chromosomal defect (these were excluded in the analysis), congenital hypothyroidism	525	<p>No increased risk of major malformations Adjusted OR 1.7 (95% CI 0.9-3.3)</p> <p>Rate of cardiovascular malformations was 3 times the background rate of the Finnish population; no statistical analysis done</p>	<p>No data on cardiovascular malformations</p> <p>Potential confounders such as maternal obesity, alcohol, and illicit drug use were not controlled for</p>
<p><b>Study 7</b> Alwan 2007 Case-control Study</p> <p>National Birth Defects Prevention Study data, U.S.A.</p>	78%	Not defined	<p>Major malformations: No. of cases exposed to fluoxetine: 76/9,622</p> <p>Cardiovascular Defects No. of cases exposed to fluoxetine: 33/9,622</p>	<p>No increased risk of major malformations or cardiovascular malformations</p> <p>Increased risk for craniosynostosis: adjusted OR 2.8 (95% CI 1.3 to 6.1)</p>	<p>Small number of cases</p> <p>Did not adjust for multiple comparisons</p> <p>Recall bias</p> <p>Underlying depression not controlled for</p>

**Appendix B: Tabular Summary of Population Based Studies on Fluoxetine Exposure During the First Trimester of Pregnancy**

Study	Quality Rating	Outcome Definition	Fluoxetine Sample Size	Study Results	Limitations
<p><b>Study 8</b> Louik 2007 Case-control study</p> <p>Slone Epidemiology Center Birth Defects Study U.S.A.</p>	76%	<p>Major malformations: craniosynostosis, omphalocele, and defects that were present in at least 100 subjects overall and at least 5 exposed subjects</p> <p>Cardiovascular malformations: categorized into 7 developmental groups</p>	<p>Major Malformations: No. of cases exposed to fluoxetine not provided No. of controls exposed to fluoxetine: 61/5860</p> <p>Cardiovascular Defects: No. of cases exposed to fluoxetine: 31/3724 No. of controls exposed to fluoxetine: 61/5860</p>	<p>No increased risk of major malformation, cardiac defects overall, or specific cardiac defects</p>	<p>Small number of cases</p> <p>Did not adjust for multiple comparisons</p> <p>Recall bias</p> <p>Underlying depression not controlled for</p>
<p><b>Study 9</b> Pederson 2009 Prospective cohort study</p> <p>Danish Registry</p>	Not rated	<p>Major malformations based on Eurocat categorization</p> <p>Cardiovascular malformations: categorized into 7 developmental groups, as per Louik</p>	348	<p>No increased risk of major malformations overall or cardiac malformations</p> <p>Having a prescription filled for more than 1 type of SSRI showed an increased risk of septal heart defects Adjusted OR 4.70 (95% CI 1.74- 12.7</p>	<p>Did not adjust for multiple comparisons</p> <p>Actual exposure was not confirmed</p> <p>Underlying depression and maternal illnesses were not controlled for</p>
<p><b>Study 10</b> Merlob 2009 Prospective cohort study</p> <p>Israel</p>	Not rated	<p>Syndromic heart defects, functional murmurs, isolated persistent foramen ovale, isolated peripheral pulmonic stenosis, and isolated patent ductus arteriosus were excluded</p>	66	<p>Increased risk of mild congenital heart defects (RR 2.17; 95% CI: 1.07-4.39) associated with first- trimester SSRI exposure</p> <p>Analysis for fluoxetine was not done</p>	<p>Small sample size</p> <p>Maternal obesity and race were not controlled for</p>

**Appendix B: Tabular Summary of Population Based Studies on Fluoxetine Exposure During the First Trimester of Pregnancy**

<b>Study</b>	<b>Quality Rating</b>	<b>Outcome Definition</b>	<b>Fluoxetine Sample Size</b>	<b>Study Results</b>	<b>Limitations</b>
<b>Study 11</b> Kallen 2007 Retrospective cohort study  Swedish health registers	Not rated	Included minor malformations of little clinical significance	919	No increased risk of malformations or cardiac malformation	Underlying diseases were not controlled for  It's not clear if outcomes were confirmed with medical records  Incomplete information on timing of exposure and dose
<b>Study 12</b> United Health Care study 2008 Retrospective cohort study  United Health Care claims data for GSK U.S.A.	Not rated	Not defined	1,292	No increased risk of major malformations or cardiac malformation	Actual exposure was not confirmed

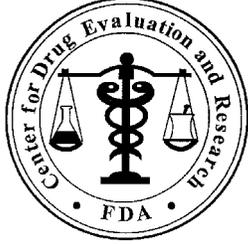
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/s/  
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LEYLA SAHIN  
06/09/2010

Karen B FEIBUS  
06/09/2010  
I agree with the content and recommendations contained in this review.

LISA L MATHIS  
06/14/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: April 20, 2010

To: Thomas Laughren, M.D.,  
Division Director, Division of Psychiatric Products

Through: Solomon Iyasu, M.D., M.P.H.,  
Division Director, Division of Epidemiology

Through: Simone Pinheiro, Ph.D., M.Sc., M.A.,  
Acting Team Leader, Division of Epidemiology

From: Fatmatta Kuyateh, M.D., M.S.,  
Medical Officer, Division of Epidemiology

Subject: Review of “Analysis, Results, and Label Language Proposal following a Meta-Analysis of Published Epidemiological Studies to Assess the Effect of Fluoxetine Exposure During the First Trimester of Pregnancy and the Risk of Major Malformations”

Drug Name(s): Fluoxetine, Prozac

Application Type/Number: NDA 018936/SLR-093

Applicant/sponsor: Eli Lilly

OSE RCM #: 2010-219

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## EXECUTIVE SUMMARY

This document is a review of a meta-analysis conducted by Eli Lilly and Company of epidemiological studies regarding fluoxetine exposure during the first trimester of pregnancy and birth outcomes of major congenital malformations and cardiovascular defects. Eli Lilly submitted a Changes Being Effected label supplement on November 6, 2009 proposing to include revisions to the Pregnancy section labeling language concerning clinical risks from in-utero exposure to fluoxetine based on their findings of a “potential risk of cardiovascular defects which Eli Lilly deems to be clinically important information for the prescribing physician.” The Division of Psychiatric Products requested that the Division of Epidemiology (DEPI) within the Office of Surveillance and Epidemiology (OSE) review the meta-analysis report and provide input on the sponsor’s proposed labeling changes. DEPI incorporated into this review of the meta-analysis report, methodology and results information obtained from a qualitative assessment of the individual studies included in the meta-analysis, and a feasibility assessment of conducting the meta-analysis, both provided by Eli Lilly.

The meta-analysis included eight published observational studies. The results of the meta-analysis suggest an increased risk of major congenital anomalies in women who were exposed to fluoxetine during the first trimester of pregnancy compared to women who did not use fluoxetine during pregnancy, although the association was not statistically significant [OR=1.34; 95% CI (0.98-1.83)]. The results also suggest a nearly 3-fold increased risk of cardiovascular defects among infants born to women who used fluoxetine during the first trimester of pregnancy compared to women who did not use fluoxetine during pregnancy (OR: 2.92; 95%CI 1.29 – 6.58). Based on further post-hoc analyses that analyzed only the noncardiac malformation data, the sponsor concluded that the positive point estimates for major malformations were driven by cardiovascular defects.

Concerning the quality of the meta-analysis, the study design was appropriate for the stated objectives, heterogeneity and publication bias were evaluated, and extensive analyses were conducted including primary analyses, sensitivity analyses, and post-hoc analyses. However, only published studies in English were included and no confounders were controlled for, thus severely limiting the interpretation of the results. Other limitations include potential misclassification of outcome and variations in exposure definitions.

DEPI’s review of the meta-analysis and the individual constituent studies found trends towards an increased risk of major congenital malformations in infants of women who used fluoxetine during the first trimester of pregnancy. The results of the meta-analysis support previous findings by Diav-Citrin et al.<sup>3</sup> of an increased risk of cardiovascular defects among infants of women who used fluoxetine during the first trimester of pregnancy. However, because of unadjusted confounding, the results of this meta-analysis do not provide definitive information to support any direct or causal associations. Thus DEPI concludes that the findings of this meta-analysis alone are not sufficient to implement the labeling changes proposed by Eli Lilly. Further evaluation of the individual studies may provide more useful information for implementing any regulatory action concerning fluoxetine and major congenital malformations or congenital heart defects.

## 1 BACKGROUND

Fluoxetine (NDA 018936) is a selective serotonin reuptake inhibitor first approved in 1987. Fluoxetine is indicated for the acute and maintenance treatment of Major Depressive Disorder, Obsessive Compulsive Disorder, Bulimia Nervosa, Panic Disorder, and Bipolar Disorders. On November 6 2009, Eli Lilly and Company (sponsor) submitted a Changes Being Effected label supplement proposing to include revisions to the Pregnancy section labeling language concerning clinical risks from in-utero exposure to fluoxetine. The new language is as follows:

(b) (4)

The meta-analysis was conducted by the sponsor, at the request of the United Kingdom's Medicines and Health Research Committee. The MHRA's request was prompted by the findings of a study by Diav-Citrin et al<sup>3</sup> (which is included in this meta-analysis) that suggested an increased risk of cardiovascular defects in infants of women who used fluoxetine during the first trimester of pregnancy compared to those who did not.

The Division of Psychiatric Products requested that the Division of Epidemiology (DEPI) within the Office of surveillance and Epidemiology review the meta-analysis report and provide input on the sponsor's proposed labeling changes.

## 2 REVIEW METHODS AND MATERIALS

### 2.1 MATERIALS REVIEWED

The following document is the focus of this review:

- Analysis, Results, and Label Language Proposal following a Meta-Analysis of Published Epidemiological Studies to Assess the Effect of Fluoxetine Exposure During the First Trimester of Pregnancy and the Risk of Major Malformations

Additional supporting information was obtained from the following reports provided by the sponsor:

- Fluoxetine Exposure During the First Trimester of Pregnancy and the Risk of Major Congenital Malformations: A qualitative Literature Review of Epidemiological Studies

(b) (4)

- Feasibility Assessment of Conducting a Meta-Analysis of Published Epidemiological Studies Regarding Fluoxetine Exposure During the First Trimester of Pregnancy and the Risk of Major Congenital Malformations

## **2.2 METHODS**

A qualitative review of the meta-analysis was conducted, evaluating the study objectives, design, measurement methods, and analyses and results for validity and usefulness for making regulatory decisions.

## **3 RESULTS OF REVIEW**

### **3.1 OBJECTIVES**

#### **3.1.1 Actual Objective**

The objective of this meta-analysis was to assess the association of fluoxetine exposure during the first trimester of pregnancy and the risk of major congenital malformations with a particular focus on cardiac defects.

#### **3.1.2 DEPI Comments on Actual Objectives**

The stated objective is appropriate and relevant.

### **3.2 STUDY DESIGN**

#### **3.2.1 Actual Design**

The study is a meta-analysis of published studies to assess the risk of major congenital malformations and cardiac defects with fluoxetine exposure during the first trimester of pregnancy. Only published cohort and case-control studies with an internal comparison group that was not exposed to fluoxetine were eligible for inclusion in the meta-analysis.

#### **3.2.2 DEPI Comments on Actual Design**

The study design is appropriate for the study objective. If, however, the published studies are systematically different from the unpublished studies, publication bias could result, thus biasing the summary estimates derived in the meta-analysis.

### **3.3 INFORMED CONSENT**

#### **3.3.1 Actual Informed Consent**

Not applicable.

#### **3.3.2 DEPI Comments on Actual Informed Consent**

Not applicable.

### **3.4 DATA SOURCE(S)**

### **3.4.1 Data Source(s)**

A search of the literature up to April 7 2009 using PubMed and EMBASE was performed to identify cohort and case-control studies assessing the risk of major congenital malformations and/or cardiac defects and fluoxetine exposure during the first trimester of pregnancy. The obtained publications were also examined to identify additional references. Out of 2850 articles initially identified, 8 met all the inclusion and exclusion criteria [APPENDIX I].

Two reviewers independently assessed the inclusion of publications and extracted relevant information from included studies using a standardized publication screening form and data extraction form. A third reviewer served as arbitrator to resolve any discrepancies.

The quality of papers was assessed based on a 27-item checklist developed by Downs and Black<sup>1</sup> that measures the quality of publications from the perspectives of reporting, external validity, internal validity, and power.

### **3.4.2 OSE Comments on Actual Data Sources**

The search for published studies was thorough and the sources used were appropriate. The inclusion/exclusion criteria were set *a priori* thus reducing the introduction of study selection bias. However, 317 articles not published in English were excluded, thus potentially introducing some publication bias. The measures of study quality were not used directly in any of the analyses (for instance for weighting or stratification).

## **3.5 STUDY TIME PERIOD(S)**

### **3.5.1 Study Time Period(s)**

The search included literature published up until April 7 2009. The studies included in the meta-analysis were published between 1993 and 2009. Exposure dates ranged from 1989 to 2005 for the cohort studies that reported this information. The range of dates for birth outcomes in the case-control studies was 1993 to 2004.

### **3.5.2 OSE Comments on Actual Study Time Period(s)**

The search included the widest possible period at the time. In addition, the range of dates for which data were collected cover a large period, making the study more generalizable.

## **3.6 POPULATION**

### **3.6.1 Population**

The geographic areas covered by the studies include North America, Europe (Italy, Germany and Finland), and Asia (Israel). The mothers' mean age ranged from 30 to 32. Women with single and multiple gestations were included in the studies.

### **3.6.2 OSE Comments on Actual Population**

The study populations were geographically diverse. On one hand, this diversity could make the results of the meta-analysis more generalizable. However, this also raises the issue of unmeasured confounders that are possibly associated with the outcomes and that may vary by geographic region. Instead of mean age, the maternal age range and percentages in each age group would have been more useful measures to report for characterizing population diversity, especially as maternal age is highly associated with major congenital anomalies.

## **3.7 EXPOSURE**

### **3.7.1 Exposure**

The exposure of interest for this meta-analysis was fluoxetine during the 1<sup>st</sup> trimester of pregnancy. Exposure was ascertained via a combination of maternal reports, medical records, and prescription databases. Because of the difference in individual study designs, the unexposed group included women who were not exposed to fluoxetine during the pregnancy, women who were exposed to drugs not known to be teratogenic, and women who were exposed to non-SSRI antidepressants.

### **3.7.2 OSE Comments on Actual Exposure**

The studies all had a common concept of exposure period during the first trimester of pregnancy, although measurement methods varied. In particular, studies that relied on maternal reporting of exposure may suffer from exposure misclassification likely to bias the summary estimates towards the null, however, this bias may not outweigh that introduced by lack of adjustment for important confounders such as tobacco, alcohol, or illicit drug use. The meta-analysis did not report on dosage or duration of use that could have provided a more granular evaluation of any possible association. The issue of inconsistent unexposed groups across the individual studies raises concerns of combinability of studies for the purpose of this meta-analysis.

## **3.8 DISEASE OUTCOME OF INTEREST**

### **3.8.1 Disease Outcome of Interest**

The primary outcomes of interest for this meta-analysis were major congenital malformations and cardiac defects. Outcomes were ascertained via various methods including reports from mothers with or without medical record confirmation, blinded and unblinded physician examination, health databases, and birth defect surveillance systems.

### **3.8.2 OSE Comments on Actual Disease Outcome of Interest**

The authors did not strictly define the outcomes, and the definitions varied across the individual studies included in the meta-analysis. In addition, outcomes were not validated in some of the individual studies. These variations in outcome definitions generate inherent inconsistencies within the meta-analysis itself, making it difficult to interpret the results.

## **3.9 SAMPLE SIZE**

### **3.9.1 Sample Size**

Among the cohort studies, there were 1861 participants exposed to fluoxetine during the first trimester, and 111953 unexposed participants in the six cohort studies. The case-control studies provided 19471 cases of major congenital malformations and 9952 controls without major malformations.

### **3.9.2 OSE Comments on Actual Sample Size**

The sample size for the primary analysis, which included only the cohort studies, was quite large although it is not clear whether it is large enough to detect an appreciable difference in the outcomes, as a priori power calculations are not typically done for meta-analysis. Based on previous power calculations for a prospective cohort design, a sample size of about 800 women

were needed to rule out a 2-fold increase in risk of congenital anomalies<sup>2</sup>. Thus, based on these assumptions one could say the primary analyses of this meta-analysis (which include only the cohort studies) would have enough power to detect a meaningful increased risk of congenital anomalies. However, considering the variations in study designs and other possible biases in the individual studies included in this meta-analysis, the studies cannot simply be collapsed to obtain adequate power; a larger sample size may be needed compared to a single cohort study. Therefore, in this situation, adequate power cannot be used to justify the finding of no association between first trimester fluoxetine use and major congenital malformations.

### **3.10 ANALYSES AND STUDY RESULTS**

The authors identified eight studies that met inclusion criteria for the meta-analysis<sup>2-9</sup>. The studies include four prospective cohort studies (Studies 1-4), two retrospective cohort studies (Studies 5-6), and two case-control studies (Studies 7-8) [APPENDIX II]. Study 8 was not included in the analyses evaluating major malformations because it was not possible to extract the exact number of infants with major congenital malformations who were exposed to fluoxetine. Studies 1 and 6 were not included in the analyses for evaluating cardiac defects due to lack of specific data about the outcome. Result summaries are shown in Appendices III and IV and forest plots in Appendices V and VI.

#### **3.10.1 Analyses**

Raw data were collected from the eight cohort and case-control studies that were included in the meta-analysis and analyzed in various combinations for primary and secondary statistical analyses. The primary analyses conducted for each of the outcomes, major congenital anomalies and cardiac defects, included only data from the cohort studies.; data from the case-control studies were not included in these primary analyses because of differences in study designs and study methods. A priori-specified secondary analyses, again for each outcome, included sensitivity analyses stratified by study type (i.e. prospective cohort, retrospective cohort, case-control), and post-hoc analyses combining raw data from the cohort and case-control studies identified for inclusion in the meta-analysis.

Primary analyses were conducted to assess the association of fluoxetine exposure during the first trimester with an outcome measure of odds ratio (OR) using logistic random effects regression model. Data from all six cohort studies were analyzed in the primary analysis of major congenital malformations. However, due to lack of data about specific cardiac defects, only four of the cohort studies were included in the primary analysis of cardiac defects.

Sensitivity analyses were performed to investigate the robustness of the primary analysis and to evaluate the variability of results from study to study. Summary estimates were obtained for the prospective cohort studies and retrospective cohort studies as separate groups. Additionally, in order to examine the influence of each individual study on the summary estimates, a “leave one out” analysis was conducted by repeating the analysis 6 times and leaving out one study each time. Both fixed and random effects models were used.

Post hoc analyses were performed for major congenital anomalies (Studies 1-7) and cardiac defects (Studies 2-5, 7 and 8) to further compare the association between fluoxetine exposure during the first trimester of pregnancy and pregnancy outcomes of major malformation/cardiac defects. Study 8 was not used in the major malformations post hoc analyses because it was not possible to extract the exact number of infants exposed to fluoxetine with major malformations due to multiple counting of some infants who had more than one major malformation. For similar reasons, Studies 1 and 6 were not included in the analyses of cardiac defects. Additional post-hoc

analyses were performed to analyze the non-cardiac defects data to evaluate the effect of the risk cardiac defects on the risk of major congenital malformations.

Heterogeneity was assessed using the Breslow-Day test for variability of effect size estimates and by visual inspection of the forest plots. Publication bias was assessed by using funnel plots and Begg's test with a p-value of <0.1 considered statistically significant.

### **3.10.2 Study Results for Major Congenital Malformations**

The primary analysis suggests a 34% increase in risk of major congenital malformation among women exposed to fluoxetine during the first trimester of pregnancy compared to women who were not exposed to fluoxetine, although these estimates did not reach statistical significance [OR = 1.34; 95% CI (0.98 – 1.83); p=0.062]. When the studies were stratified by study type (prospective/retrospective cohort) for sensitivity analyses, the random effects model results were similar to the primary analysis results but again the findings were not statistically significant. The fixed effects model results for prospective cohort studies [OR=1.72; 95% CI (1.09 – 2.91); p=0.022] and all cohort studies [OR=1.36; 95% CI (1.07 – 1.72; p=0.012] were both statistically significant.

In order to better understand if the estimates for major congenital malformations were driven by the effects of cardiac defects, additional post hoc analysis of data from studies reporting cardiac defects separately (Studies 2-5) was conducted. Only data for non-cardiac major congenital malformations was used. The results did not show a significant association between fluoxetine and non-cardiac major congenital malformations [OR=0.91; 95% CI (0.50-1.68); p=0.671], and the point estimate was pulled towards the null compared to the primary analysis result regarding all major congenital anomalies.

In the “leave out one” analyses, both random and fixed effects models showed that Study 5, the study with the largest sample size and with one of the highest quality scores (70%), had the greatest impact on the summary odds ratio by moderating it towards the null. Study 5 is a retrospective cohort study and had a positive but not statistically significant finding.

In post hoc analyses, raw data from Studies 1 through 7 were combined for a post hoc analysis which showed significant association between fluoxetine use during the first trimester of pregnancy and major congenital malformations, for both random and fixed effects models [OR=1.32; 95% CI (1.05 – 1.66); p=0.018].

The Breslow-Day test for heterogeneity of effect size estimates of the six cohort studies showed no strong evidence of inter-study heterogeneity. Heterogeneity was not assessed for the case-control studies (Studies 7 and 8). A funnel plot was constructed for Studies 1 -7 to examine publication bias. The plot showed some evidence supporting the existence of publication bias as symmetrical distribution of estimated odds ratios around the summary odds ratios from the primary analysis was not observed. However, the Begg's test was not statistically significant (p=0.76).

Based on these results the investigators concluded that there was a possible association between fluoxetine use during the first trimester of pregnancy and an increased risk of major malformations, but that this association was mainly driven by the increased risk of cardiac defects.

### 3.10.3 Study Results for Cardiac Defects

Primary analysis of cardiovascular defects data (Studies 2-5) showed a statistically significant odds ratio for cardiac defects in women with fluoxetine during the first trimester of pregnancy compared to women not exposed to fluoxetine [OR = 2.92; 95% CI (1.29 – 6.58); p=0.025]. When the studies were stratified by study type, the summary estimates of the case control studies were not consistent with the primary analysis results [OR=0.63; 95% CI (0.39-1.03); p=0.066].

Both random and fixed effects models in the “leave out one” analyses showed that the study (Study 5) with the largest sample size had the greatest impact on the summary odds ratio by moderating it towards the null.

Post hoc analysis of data from the cohort studies (Studies 2-5) and case-control studies (Studies 7 and 8) combined had a point estimate that was smaller than that of the primary analysis and did not reach statistical significance [OR=1.23; 95% CI (0.60 – 2.53); p=0.573 in random effects model].

The Breslow-Day test for heterogeneity suggested that the four cohort studies were homogeneous amongst themselves (p=0.25). However, the group of case-control studies had effect sizes in a direction opposite that in the cohort studies. When data from the cohort and case control studies were combined, there was statistical evidence of heterogeneity suggesting a significant variability between effect size estimates from cohort studies and those from case-control studies. A funnel plot showed some evidence of publication bias as symmetrical distribution of estimated odds ratios around the summary OR from the primary analysis was not observed. However, the Begg test was not statistically significant (p=0.71).

### 3.10.4 OSE Comments on Analyses and Study Results

The sponsor conducted extensive analyses, which included primary meta-analyses of each outcome, and sensitivity, and post hoc analyses. Random effects models were used as the primary models for cardiac outcomes because of the heterogeneity observed among the studies. Although heterogeneity was not formally assessed across all of the studies used in the analyses of major malformations, and heterogeneity was not observed across studies that were assessed, the use of a random effects model is reasonable if the intent is to make unconditional inferences and generalize the results beyond the included studies, and if these criteria were specified *a priori*<sup>10</sup>.

Visual assessments of the funnel plots revealed some evidence of publication bias, but these conclusions may be misleading as the funnel plots only included a small number of studies (6 for cardiac defects and 7 for major congenital malformations), and a sufficient number of studies is usually required for such assessments to be accurate. Consequently it is not surprising that the Begg test was not statistically significant for either of the outcomes, because statistical tests of publication bias in meta-analyses are often underpowered. As a result, we cannot be certain of the extent to which the summary estimates derived from these analyses are subject to publication bias.

Primary analyses for major congenital malformations and cardiac defects did not include the case control studies. This is especially important because the results of the *a priori*-specified post hoc analyses, which include the case control studies, disagree with the primary analyses results for both outcomes. The post hoc analyses for major malformations suggest a statistically significant increase in risk among women exposed to fluoxetine compared to unexposed women [OR=1.32; 95% CI (1.05-1.66)]; primary analysis suggests an increased risk but the finding did not reach statistical significance [OR=1.34; 95% CI (0.98-1.83)]. The post hoc analyses for cardiac defects

suggest a much smaller increase in risk among women exposed to fluoxetine compared to unexposed women [OR=1.23; 95% CI (0.60-2.53)], while primary analysis suggested a larger and statistically significant increase [OR=2.92; 95% CI 1.29-6.58]. Clearly the case-control studies have a large impact on the results of these analyses, possibly due to point estimates that fall below 1.0. The case control studies each suggested a decreased risk of cardiovascular defects among women exposed to fluoxetine [OR(95%CI) = 0.48 (0.29-0.80) and 0.80(0.52-1.23) for Study 7 and Study 8 respectively] compared to women not exposed to fluoxetine. The unexposed group in one of the case-control studies (ref) included women who were exposed to non-SSRI antidepressants, which could account for the observed protective effect of fluoxetine in this study. The results of these analyses thus highlight the need for an exploration of the sources of heterogeneity and for more in-depth evaluations of the individual studies included in the meta-analysis.

Sensitivity analyses, in particular the leave-one-out analyses of the cohort studies, suggested that Study 5 had the largest impact on the primary analysis summary estimates for major congenital malformations and cardiac defects by pulling the estimates towards the null. Study 5, is a population based retrospective cohort study conducted in British Columbia using administrative claims data. The sample size of 107958 was the largest sample size among the studies included. The study found no association between fluoxetine exposure during first trimester of pregnancy and major congenital malformations or cardiac defects. Though fairly well conducted and adequately powered, Study 5 was limited by the inability to verify diagnoses of congenital malformations thus raising the question of misclassification bias, which if present would likely be non-differential, tending to bias the estimates towards the null. The study was also limited by lack of adjustment for potential confounders such as tobacco, alcohol, or illicit drug use, although one would expect the point estimate then to be pulled away from the null without such adjustments because treated patients might be more likely to smoke, drink alcohol, or use illicit drugs<sup>11,12</sup>.

Overall, the results of this meta-analysis suggest trends towards an association between fluoxetine use during the first trimester of pregnancy and major congenital malformations and congenital cardiac defects. The meta-analysis has several strengths including pre-defined methods for data collection, and data abstraction by two independent epidemiologists. In general a meta-analysis of several studies (of which at least one reached statistical significance) with a positive finding would strengthen the overall evidence<sup>13</sup>.

However, caution must be exercised in drawing conclusions about the nature and strength of the association between fluoxetine and major congenital anomalies and congenital heart defects based on the results of this meta-analysis for several reasons. A major limiting factor of this meta-analysis is that potential confounder information (tobacco and substance abuse, other medical diagnoses, family history congenital birth defect, maternal weight gain, etc) was not collected and accounted for during analyses, thus potentially leading to an overestimation of the association between fluoxetine and birth defects. for reasons mentioned above. In addition, since the unexposed groups comprised mostly of non-depressed women, the possible effects of depression on outcomes were not accounted for. The definitions of outcomes were not uniform across the studies included in the meta-analysis and some outcomes were not verified, thus possibly introducing a source of misclassification bias that is likely non-differential and may bias the summary estimates towards the null. Unpublished studies or studies published in a language other than English could have valuable data that were missed by this meta-analysis and this omission could bias the derived summary estimates if these studies are systematically different from the published studies. Finally, efforts were not made to inquire about and obtain vital outcome information (if available) from Studies 1 and 6 which were excluded from the cardiac defects

analyses and the non-cardiac malformations post hoc analyses because information on cardiac defects could not be obtained from the publications.

## 4 CONCLUSION AND RECOMMENDATIONS

### 4.1.1 Conclusion

In summary, the results of this meta-analysis suggest an increased risk of cardiovascular defects among infants of women exposed to fluoxetine during the first trimester of pregnancy. In addition, the results show trends towards an association between fluoxetine use during the first trimester of pregnancy and major congenital malformations. However, due to unmeasured confounding, one cannot trust that these associations found in this study are real. (b) (4)

incomplete and might not be based on strong epidemiologic evidence.

The findings of this meta-analysis alone are not sufficient to implement the labeling changes proposed by the sponsor without thorough benefit-risk assessment of implementing such labeling changes for the following reasons:

- The meta-analysis has several limitations that make it difficult to draw definitive conclusions from this study about the association between fluoxetine use during first trimester of pregnancy and major congenital malformations or cardiac defects..
- A meta-analysis of observational studies is greatly limited by the inherent biases of each individual study that are carried over and combined in the meta-analysis.
- Untreated depression in pregnancy can have serious consequences to both mother and fetus<sup>14</sup>, therefore there is a potential public health burden to consider before restricting treatment of such a group.

### 4.1.2 Recommendation

Further evaluation of the individual studies may provide more useful information for implementing any regulatory action concerning fluoxetine and major congenital malformations or congenital heart defects.

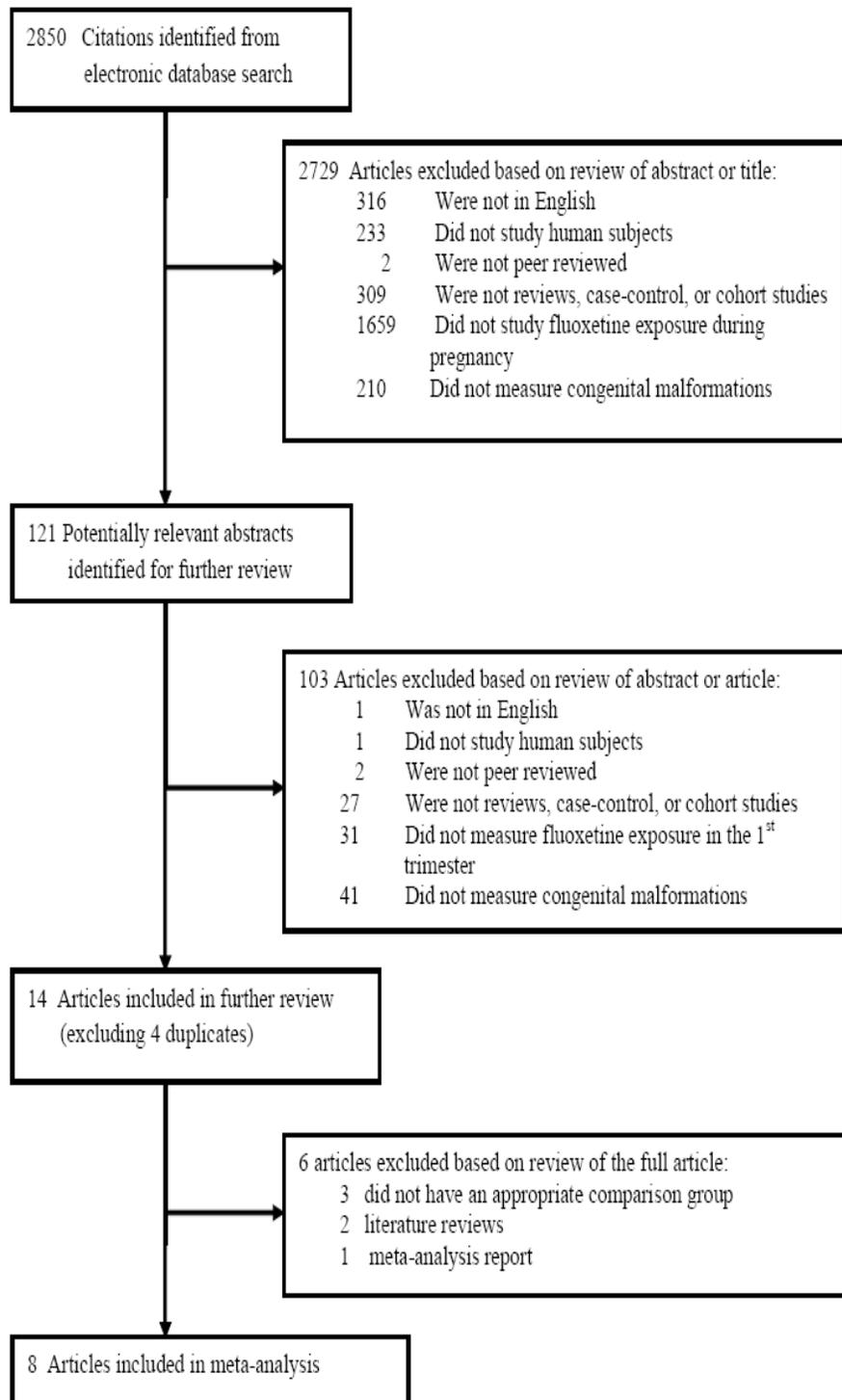
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## APPENDICES

### APPENDIX I. Study Selection Flow Chart.



**APPENDIX II. Summary of Studies Included in the Meta-analysis.**

Study	Study Design and setting	Study Quality Rating	Exposure and Outcome Definitions				Sample Size	No. of Malformations/No. of Group	Strengths and Limitations*
			Exposure	Comparator	Major Malformation	CV Defect			
Study 1 Einarson et al., 2009	Prospective cohort study  Teratogenic information service, Canada  Study period NR†	39%	Fluoxetine exposure during the 1st trimester	Non-teratogens and not exposed to AD‡	NR	NR	Fluoxetine: n=61  Non-antidepressant: n=928	Major Malformations: Fluoxetine exposure group: 3/61 Comparator group: 25/928  Cardiovascular Defects: Fluoxetine exposure group: 2/61 Comparison group: not provided	Outcomes were medically confirmed.  Low quality score mainly due to small sample size of fluoxetine group.  Drug exposure and potential risk factors were self-reported.  The effects of underlying diseases and other risk factors were not controlled in analyses.  Lacked enough sample size to analyze fluoxetine exposure group.
Study 2 Diav-Citrin et al., 2008	Prospective cohort study  Teratogenic information service, Israel, Italy, and Germany  Study period: 1994-2002 in Israel and Italy, 2002-2005 in Germany	52%	Fluoxetine exposure during the 1 <sup>st</sup> trimester	Nonteratogen exposure during pregnancy	Structural abnormalities in the offspring that have serious medical, surgical, or cosmetic consequences.	NR	Fluoxetine group: 346  nonteratogenic exposure: 1467	Major Malformations: Fluoxetine exposure group: 15/253 Comparator group: 40/1359  Cardiovascular Defects: Fluoxetine exposure group: 7/253 Comparator group: 8/1359	Self-reported exposure information.  Self-reported and physician-reported outcomes.  Large loss to follow-up rate in fluoxetine group (13 to 56% across diff sites).  Did not control for effects of maternal illness, alcohol, and socioeconomic status.
Study 3 Chambers et al., 1996	Prospective cohort study.  Teratogenic information	59%	Fluoxetine exposure during the 1 <sup>st</sup> trimester.	Nonteratogen exposure during pregnancy	A structural defect occurring in less than 4% of the general population that	NR	Fluoxetine: 164  Comparator: 226	Major Malformations: Fluoxetine exposure group: 9/164 Comparator group: 9/226  Cardiovascular Defects:	Outcomes were reported by mothers and 98.5% were confirmed with medical records

Study	Study Design and setting	Study Quality Rating	Exposure and Outcome Definitions				Sample Size	No. of Malformations/No. of Group	Strengths and Limitations*
			Exposure	Comparator	Major Malformation	CV Defect			
	service, US. Study Period: 1989-1995				has cosmetic or functional importance.			Fluoxetine exposure group: 3/164 Comparator group: 1/226	Self-reported exposure information.  Small sample size.  Small numbers of outcomes made it unfeasible to control for potential confounders
Study 4 Pastuzak et al., 1993	Prospective cohort study.  Teratogenic information service, Canada and USA.  Study period: NR	50%	Fluoxetine exposure during the 1 <sup>st</sup> trimester	Nonteratogen exposure	NR	NR	Fluoxetine: 98 Comparator: 110	Major Malformations: Fluoxetine exposure group: 2/98 Comparator group: 2/110  Cardiovascular Defects: Fluoxetine exposure group: 1/98 Comparator group: 2/110	Small study size limits ability to rule out minimal increased risk above baseline.  Self-reported exposure.  Outcomes were reported by mothers and corroborated with written documentation from the child's physician.  Did not adjust for potential confounders.
Study 5 Oberlander et al., 2008	Retrospective cohort study  Health administrative data sources, Canada Study period: 1997-2002	70%	Fluoxetine exposure in the 1 <sup>st</sup> trimester	No prescription for SSRI or benzodiazepine in the first trimester	ICD9 codes 740.0-759.9, excluding the following minor anomalies: 743.6, 744.1, 744.2-744.4, 744.8, 744.9, 747.0, 747.5, 750.0, 752.4, 752.5, 754.6, 755.0, 755.1, 757.2-757.6, 757.8, 757.9, 758.4	ICD9 codes: 745.0-747.9 excluding 747.0 and 747.5.	Fluoxetine: 638 Comparator: 107,320	Major Malformations: Fluoxetine exposure group: 21/638 Comparator group: 3369/107320  Cardiovascular Defects: Fluoxetine exposure group: 5/638 Comparator group: 512/107320	Utilized ICD9 codes to indicate diagnosis and dispensing records to indicate medication use.  Not able to verify the time and validity of the outcomes and the drug exposure. No information regarding tobacco, alcohol, and illicit drug use. The effects from these factors were not controlled.
Study 6 Malm et al., 2005	Retrospective cohort study.  Four	81%	Women with at least 1 purchase of fluoxetine	Women with no reimbursed drug purchases	A significant congenital structural anomaly,	NR	Fluoxetine: 525 Comparator: 1782	Major Malformations: Fluoxetine exposure group: 29/525 Comparator group: 62/1782	Large sample size. Outcomes were from medical records. Drug dosage and timing

Study	Study Design and setting	Study Quality Rating	Exposure and Outcome Definitions				Sample Size	No. of Malformations/No. of Group	Strengths and Limitations*
			Exposure	Comparator	Major Malformation	CV Defect			
	population-based healthcare registries, Finland  Study period: 1996-2001		during the period of 1 month before pregnancy up until 12 gestational weeks	during the period covering 1 month before and throughout pregnancy	chromosomal defect, or congenital hypothyroidism		Cardiovascular Defects: Fluoxetine exposure group: 12/525 Comparator group: not provided	of drug use may not be accurate. The effects from some potential confounders such as alcohol and illicit drug use were not controlled.	
Study 7 Alwan et al., 2007	Case-control  National Birth Defects Prevention Study data, USA  Study Period: 1997-2002	78%	Use of fluoxetine from 1 month before to 3 months after conception (266 days before estimated delivery data)	No SSRI use at any time during pregnancy or during 3 months prior to conception; exposure to non-SSRI antidepressants also considered unexposed.	Infants that received a diagnosis of at least one of 4 cardiac defects or 14 noncardiac defects.  Infants with chromosomal abnormalities or single-gene conditions were excluded.	Conotruncal, septal, right ventricular outflow tract obstruction, and left ventricular outflow tract obstruction defects.	Cases: 9622  Controls: 4092  Major Malformations  No. of cases exposed to fluoxetine: 76/9622 No. of controls exposed to fluoxetine: 29/4092  Cardiovascular Defects  No. of cases exposed to fluoxetine: 33/9622 No. of controls exposed to fluoxetine: 29/4092	Recall bias in information on exposure to SSRIs and other potential risk factors which were collected from telephone interview. Participation rate was about 70%. The effects from some underlying diseases such as depression were not controlled.	
Study 8 Louik et al., 2007	Case-control study  Slone Epidemiology Center Birth Defects Study, USA  Study Period: 1993-2004	76%	Use of fluoxetine from 28 days before the last menstrual period (LMP) through the 4 <sup>th</sup> lunar month (112 days after LMP)	No exposure to any antidepressant at any time from 56 days before LMP through end of pregnancy	NR	Categorized into 7 groups: looping, laterality, and single ventricle defects; conotruncal defects; atrioventricular canal; right ventricular outflow tract obstruction; left ventricular outflow tract obstruction; septal defects; and total or partial anomalous pulmonary venous return.	Cases: 3724  Controls: 5860  Major Malformations  No. of cases exposed to fluoxetine cannot be derived from publication No. of controls exposed to fluoxetine: 61/5860  Cardiovascular Defects  No. of cases exposed to fluoxetine: 31/3724 No. of controls exposed to fluoxetine: 61/5860	Self-reported exposure and medical history during pregnancy; recall bias is a concern.  No information from about 40% of the targeted population.  Adjusted OR control for maternal lifestyle and presence of diabetes or seizures.  Not able to control for depression.  Multiple comparisons.	

\*As reported by Eli Lilly

†NR = not reported

‡AD = Antidepressant

Appears this way on the original

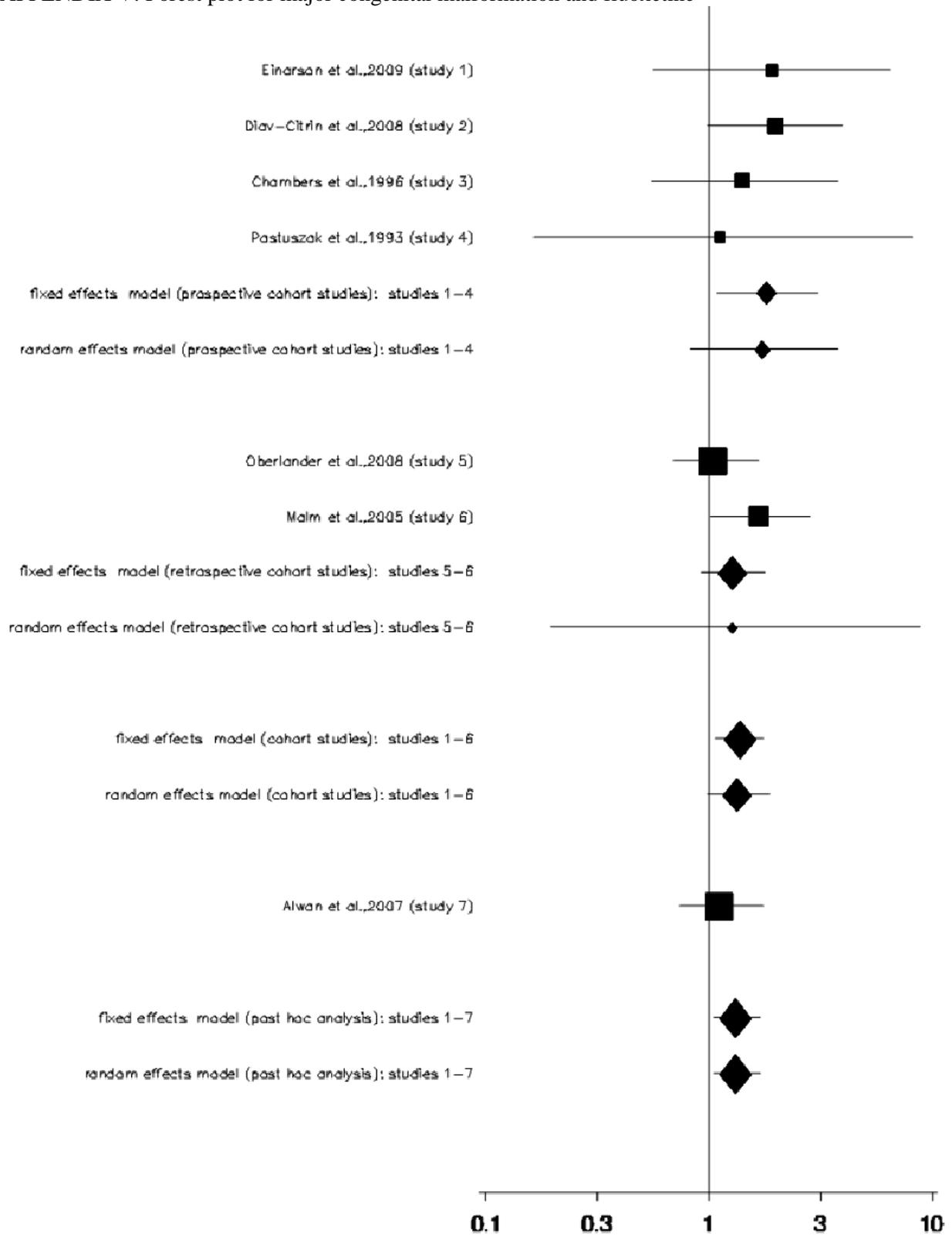
**APPENDIX III. Summary of Meta-Analysis Results: Major Congenital Malformations and Fluoxetine Exposure During the First Trimester of Pregnancy.**

<b>Method</b>	<b>Studies</b>	<b>Odds Ratio (95% Confidence Interval)</b>	<b>p-Value</b>
Primary analysis	Studies 1 – 6 (random effects model)	1.34 (0.98 - 1.83)	.062
Sensitivity analyses			
	1	1.87 (0.55 - 6.37)	.318
	2	1.94 (0.99 - 3.80)	.053
	3	1.40 (0.54 - 3.61)	.486
	4	1.13 (0.16 - 8.14)	.907
	5	1.05 (0.68 - 1.63)	.822
	6	1.66 (1.02 - 2.71)	.041
Case-control study	7	1.12 (0.73 - 1.71)	.618
Prospective cohort studies	Studies 1 – 4 (random effects model)	1.72 (0.82 - 3.64)	.103
	Studies 1 – 4 (fixed effects model)	1.78 (1.09 - 2.91)	.022
Retrospective cohort studies	Studies 5 – 6 (random effects model)	1.27 (0.19 - 8.72)	.357
	Studies 5 – 6 (fixed effects model)	1.27 (0.93 - 1.74)	.138
All cohort studies	Studies 1 – 6 (fixed effects model)	1.36 (1.07 - 1.72)	.012
Post hoc analyses			
	Studies 1 – 7 (random effects model)	1.32 (1.05 – 1.66)	.018
	Studies 1 – 7 (fixed effects model)	1.32 (1.05 – 1.66)	.018

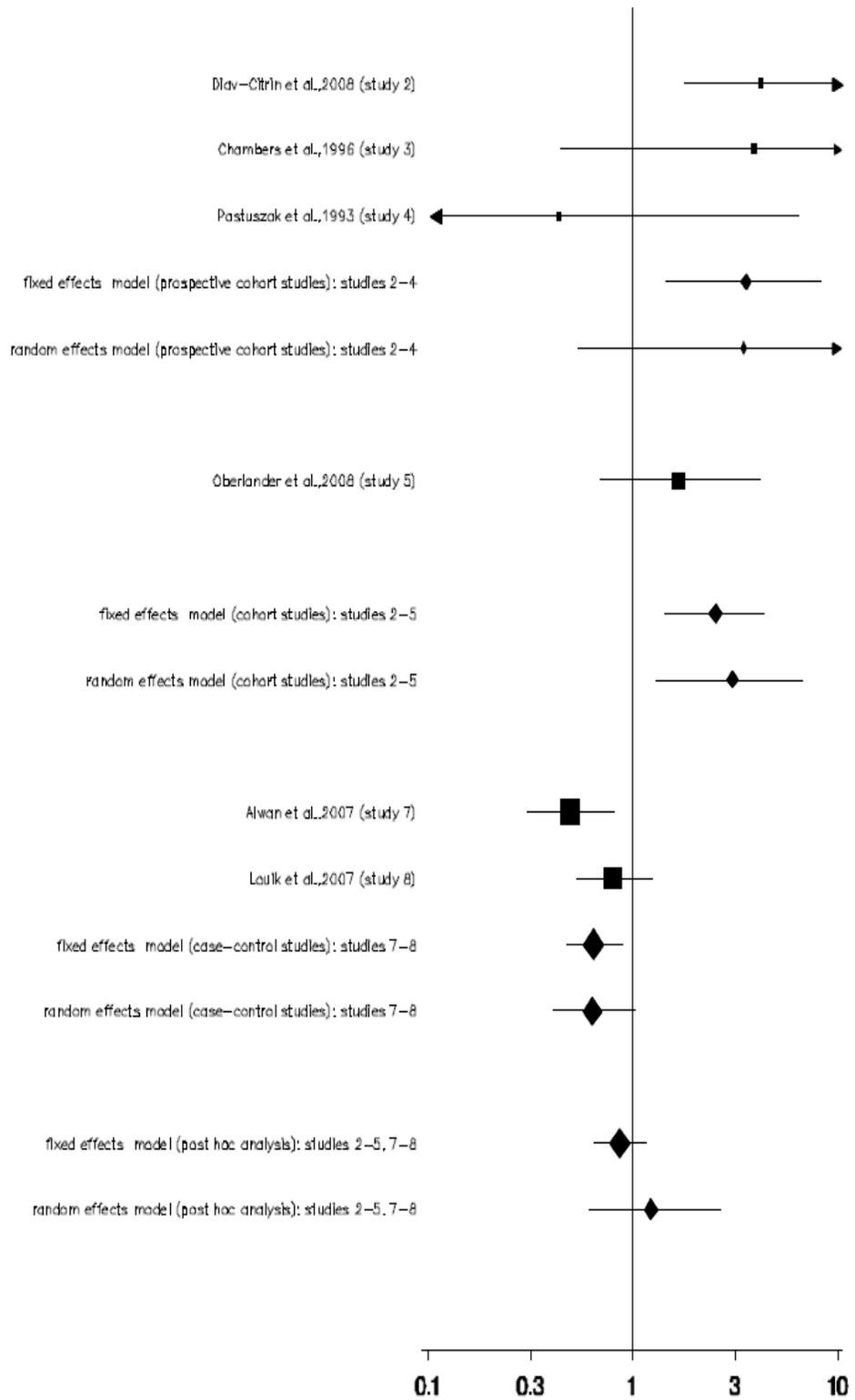
**APPENDIX IV. Summary of Meta-analysis Results: Cardiovascular Defects and Fluoxetine Exposure During the First Trimester of Pregnancy.**

<b>Method</b>	<b>Studies</b>	<b>Odds Ratio (95% Confidence Interval)</b>	<b>p-Value</b>
Primary analysis	2,3,4,5 (random effects model)	2.92 (1.29 – 6.58)	.025
<b>Sensitivity analyses</b>			
	2	4.81 (1.73 - 13.37)	.003
	3	4.19 (0.43 - 40.67)	.216
	4	0.56 (0.05 - 6.24)	.635
	5	1.65 (0.68 - 3.99)	.268
	7	0.48 (0.29 - 0.80)	.004
	8	0.80 (0.52 - 1.23)	.309
Prospective cohort studies	2,3,4 (random effects model)	3.34 (0.53 - 21.20)	.107
	2,3,4 (fixed effects model)	3.43 (1.42 - 8.29)	.006
All cohort studies	2,3,4,5 (fixed effects model)	2.44 (1.41 – 4.20)	.001
Case –control studies	7,8 (random effects model)	0.63 (0.39 – 1.03)	.066
	7,8 (fixed effects model)	0.64 (0.46 - 0.89)	.008
<b>Post hoc analyses</b>			
	Studies 2-5, 7-8 (random effects model)	1.23 (0.60 – 2.53)	.573
	Studies 2-5, 7-8 (fixed effects model)	0.86 (0.64 – 1.15)	.307

APPENDIX V: Forest plot for major congenital malformation and fluoxetine



APPENDIX VI: Forest plot for cardiovascular defects and fluoxetine



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-18936	SUPPL-93	LILLY RESEARCH LABORATORIES DIV ELI LILLY AND CO	PROZAC

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/s/

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FATMATTA M KUYATEH  
04/20/2010

TAREK A HAMMAD  
04/20/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 18-936/S-093**

**NDA 21-235/S-016**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**From:** [Ansah, Kofi](#)  
**To:** ["Kevin C Sheehan"](#)  
**Subject:** RE: PROZAC SLRs -- NDA 18-936/S-091/S-093 & NDA 21-235/S-015/S-016  
**Date:** Tuesday, March 22, 2011 4:10:11 PM

---

Kevin,

Thank you for your prompt response. We are in agreement with your proposed changes to our proposed labeling. Please expect our letter in a week or so.

Thanks,  
Kofi.

-----Original Message-----

From: Kevin C Sheehan [[mailto:SHEEHAN\\_KEVIN\\_C@LILLY.COM](mailto:SHEEHAN_KEVIN_C@LILLY.COM)]  
Sent: Tuesday, March 22, 2011 1:25 PM  
To: Ansah, Kofi  
Subject: PROZAC SLRs -- NDA 18-936/S-091/S-093 & NDA 21-235/S-015/S-016

Kofi,

Apologize for confusion with prior e-mail as I used colored and strikethrough text in e-mail to reflect changes and apparently this may not have been reflected upon FDA receipt.

Attached is the MSWord document with changes to FDA text highlighted in yellow and in track changes.

(See attached file: proposed-draft\_chgs to FDA text (for email to FDA).doc)

We will submit proposed and clean version of this labeling in an eCTD submission to FDA tomorrow (Wednesday, Mar 23) as labeling amendment to supplements NDA 18-936/S-091/S-093 & NDA 21-235/S-015/S-016.

Kevin Sheehan, MS, PharmD  
Manager  
Global Regulatory Affairs - US  
Phone: 317-651-2520  
Fax: 317-276-1652

"Ansah, Kofi"  
<Kofi.Ansah@fda.h  
hs.gov>  
03/22/2011 10:48 AM  
Subject  
FW: PROZAC SLRs -- NDA  
18-936/S-091/S-093 & NDA  
21-235/S-015/S-016  
To  
'Kevin C Sheehan'  
<SHEEHAN\_KEVIN\_C@LILLY.COM>  
cc

Kevin,

It's unclear to us exactly what your proposed changes were to the suggested labeling. It would help if you used the attached document. Please make your proposed changes on the attached document using track changes so that we can see exactly what you are proposing. Send this back to us as soon as possible, preferably by COB today.

Thanks,  
Kofi.

-----Original Message-----

From: Kevin C Sheehan [[mailto:SHEEHAN\\_KEVIN\\_C@LILLY.COM](mailto:SHEEHAN_KEVIN_C@LILLY.COM)]

Sent: Monday, March 21, 2011 2:36 PM

To: Ansah, Kofi

Cc: Roland W Usher

Subject: Re: PROZAC SLRs -- NDA 18-936/S-091/S-093 & NDA 21-235/S-015/S-016

Kofi

Lilly is aligned with FDA's proposal except that Lilly request two edits to FDA's proposed labeling to be consistent with the Diav Citrin 2008 publication. This first proposal is to clarify the name of the group which conducted the epidemiologic study 'European Network of Teratology Information Services'. The second proposal is to clarify the labeling language to align with the authors' conclusion regarding their findings in relation to other epidemiologic reports. "This study suggests a possible association between cardiovascular anomalies and first-trimester exposure to fluoxetine." Diav Citrin 2008.

There are no adequate and well-controlled clinical studies on the use of fluoxetine in pregnant women. Results of a number of published epidemiological studies assessing the risk of fluoxetine exposure during the first trimester of pregnancy have demonstrated inconsistent results. More than 10 cohort studies and case-control studies failed to demonstrate an increased risk for congenital malformations overall. However, one prospective cohort study conducted by a Network of European European Network of Teratology Information Services demonstrated a statistically reported an increased risk of cardiovascular malformations in infants born to women (N = 253) exposed to fluoxetine during the first trimester of pregnancy compared to infants of women (N = 1,359) who were not exposed to fluoxetine. There was no specific pattern of cardiovascular malformations. Overall, however, a causal relationship has not been established.

If Lilly's edits are acceptable to FDA please respond via e-mail and we will send you word version of the full Prozac USPI as a submission to NDA 18-936.

We can also send word version of the full Prozac USPI via e-mail if it helps speed up your process to support FDA action on these outstanding supplements.

Additionally Lilly is planning to submit a new Prior Approval supplemental NDA proposing the revisions to Prozac USPI on April 8, 2011 and if possible we would like to incorporate FDA's action on NDA 18-936/S-091/S-093 & NDA 21-235/S-015/S-016 into this labeling supplement.

Lastly, I will be out of the office the week of March 28th and I'd ask that you send any Prozac correspondence during that time to Roland (Rod) Usher (USHER\_ROLAND\_W@LILLY.COM) during my absence.

Thanks  
Kevin Sheehan, MS, PharmD  
Manager  
Global Regulatory Affairs - US  
Phone: 317-651-2520  
Fax: 317-276-1652  
sheehankc@lilly.com

"Ansah, Kofi"  
<Kofi.Ansah@fda.h  
hs.gov>  
'Kevin C Sheehan'  
<SHEEHAN\_KEVIN\_C@LILLY.COM>  
03/15/2011 05:25 PM  
To  
cc  
Subject  
PROZAC SLRs -- NDA  
18-936/S-091/S-093 & NDA  
21-235/S-015/S-016

Dear Dr. Sheehan,

We have completed our review of your supplemental applications dated May 21, 2009 (NDA 18936/S-091 & NDA 21235/S-015) and November 6, 2009 (NDAs 18936/S-093 & 21235/S-016) as well as the amendments submitted to NDAs 18936/S-091 & 21235/S-015 dated November 12, 2009, and September 13, 2010.

We concur with your proposed revisions submitted on May 21, 2009. However, we do not agree with your proposed pregnancy revisions submitted on November 6, 2009. In an effort to take final action on these labeling changes, we would like to negotiate labeling with Lilly.

Attached are our proposed revisions. Please let us know within 1 week whether you concur with these changes.

If you have any questions, feel free to contact me.

Regards,  
Kofi.

-----  
Kofi Boadu Ansah, R.Ph., Pharm.D.  
CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products  
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109  
Silver Spring, MD 20993 - 0002  
Phone: (301) 796-4158  
Fax: (301) 796-9838  
Email: Kofi.Ansah@fda.hhs.gov  
Commissioned Corps of the United States Public Health Service- "Protecting,  
promoting, and advancing the health and safety of the Nation"

IMPORTANT NOTICE: This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution, disclosure, copying, or use of the information contained herein is strictly prohibited. If you think you have received this e-mail message in error, please notify the sender immediately.

(See attached file: NDA18936 Prozac\_FDA Label (S091 S093)\_031411.doc)

(See attached file: NDA18936 Prozac\_FDA Label (S091 S093)\_031411.doc)

50 Pages Immediately Following Withheld - b(4) Draft Labeling

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/s/  
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KOFI B ANSAH

08/07/2013

Archiving email exchange with sponsor to secure labeling agreement for PROZAC SLRs - NDAs 18936 S091\_S-093\_S-095 and NDA 21235 S-015\_S-016\_S-017 that were approved 4/4/2011.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Office of Surveillance and Epidemiology (OSE)</b> <b>Attention: Sandra Griffith</b>		FROM: <b>HFD-130/ Division of Psychiatry Products</b>		
DATE 1/25/10	IND NO.	NDA NO. 018936/ SLR-093	TYPE OF DOCUMENT Labeling supplement	DATE OF DOCUMENT 11/06/09
NAME OF DRUG Prozac (fluoxetine hydrochloride)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Major Depressive Disorder	DESIRED COMPLETION DATE <b>3/20/2010</b>
NAME OF FIRM: Eli Lilly and Company				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Labeling Supplement				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>  Lily submitted this CBE Labeling Supplement on November 6, 2009. In this SLR, they are proposing to include labeling language about clinical risks from in-utero fluoxetine exposure. DPP would like your input on the sponsor's proposed labeling changes. This submission contains proposed labeling as well as 3 supporting documents [all of which are attached to this consult]. The submission is also available at the following EDR link: EDR Location: <a href="\\CDSESUB1\EVSPROD\NDA018936\0020">\\CDSESUB1\EVSPROD\NDA018936\0020</a>  We would like OSE to review the data that the sponsor has analyzed to support the change. The sponsor is using the results of a meta-analysis that they have conducted, in addition to post-hoc analyses to support the statements that they have added to labeling (b) (4) a potential risk of cardiovascular defects in infants of women exposed to fluoxetine in the first trimester, but that other data are inconclusive. We deem it helpful to get input from epidemiologists who have expertise in meta-analysis methodology.  The medical reviewer from DPP is Earl Hearst, M.D. and the TL is Bob Levin, M.D. and the Maternal Health Team Reviewer from PMHS is Leyla Sahin, M.D. [and her TL is Karen Feibus, M.D.]. Please let me know if you have any questions for the Division or the sponsor.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one)		

Kofi Ansah, Pharm.D. Senior Regulatory Project Manager 301-796-4158 Kofi.ansah@fda.hhs.gov	<input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS      x HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-18936

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SUPPL-93

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LILLY RESEARCH  
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PROZAC

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/s/  
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KOFI B ANSAH  
01/27/2010

THOMAS P LAUGHREN  
01/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): Pediatric Maternal Health Staff Attention: Lisa Mathis, M.D.		FROM: HFD-130/ Division of Psychiatry Products		
DATE 12/21/09	IND NO.	NDA NO. 018936/ SLR-020	TYPE OF DOCUMENT Labeling supplement	DATE OF DOCUMENT 11/06/09
NAME OF DRUG Prozac (fluoxetine hydrochloride)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Major Depressive Disorder	DESIRED COMPLETION DATE <b>2/15/2010</b>
NAME OF FIRM: Eli Lilly and Company				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Labeling Supplement				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Lily submitted this CBE Labeling Supplement on November 6, 2009. In this SLR, they are proposing to include labeling language about clinical risks from in utero fluoxetine exposure. DPP would like your input on the sponsor's proposed labeling changes. This submission contains proposed labeling as well as 3 supporting documents [all of which are attached to this consult]. The submission is also available at the following EDR link:      EDR Location: <a href="\\CDSESUB1\EVSPROD\NDA018936\0020">\\CDSESUB1\EVSPROD\NDA018936\0020</a>  The medical reviewer is Earl Hearst, M.D. and the TL is Bob Levin, M.D. Let me know if you have any questions to send to the sponsor.				
SIGNATURE OF REQUESTER Kofi Ansah, Pharm.D. Senior Regulatory Project Manager 301-796-4158 Kofi.ansah@fda.hhs.gov		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS      x HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-18936

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SUPPL-93

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LILLY RESEARCH  
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PROZAC

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/s/  
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KOFI B ANSAH  
12/23/2009

THOMAS P LAUGHREN  
12/23/2009