CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

018936Orig1s111

Trade Name:	PROZAC
Generic or Proper Name:	(fluoxetine hydrochloride)
Sponsor:	Eli Lilly and Company
Approval Date:	October 6, 2021
Indication:	PROZAC® is a selective serotonin reuptake inhibitor indicated for: • Acute and maintenance treatment of Major Depressive Disorder (MDD) • Acute and maintenance treatment of Obsessive-Compulsive Disorder (OCD) • Acute and maintenance treatment of Bulimia Nervosa • Acute treatment of Panic Disorder, with or without agoraphobia PROZAC and olanzapine in combination for treatment of: • Acute Depressive Episodes Associated with Bipolar I Disorder • Treatment Resistant Depression.

CENTER FOR DRUG EVALUATION AND RESEARCH

018936Orig1s111

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

018936Orig1s111

APPROVAL LETTER

NDA 018936/S-111

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Richard Hoffman, MS, RAC
Advisor, Global Regulatory Affairs – US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Hoffman

Please refer to your supplemental new drug application (sNDA) dated and received July 2, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Prozac (fluoxetine) capsules.

We also refer to our letter dated June 7, 2021, notifying you, under Section 505(o)(4) of the FDCA, of new safety information pertaining to the association between the use of selective serotonin reuptake inhibitors (SSRI)/serotonin and norepinephrine reuptake inhibitors (SNRI) and the occurrence of sexual dysfunction that we believe should be included in the labeling for all SSRI and SNRI.

This supplemental new drug application provides for revisions to the labeling for Prozac consistent with our June 7, 2021, safety labeling change notification letter.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Prescribing Information 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

[21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

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, call Ermias Zerislassie, Safety Regulatory Project Manager, at 301-796-2770.

Sincerely,

{See appended electronic signature page}

Marc Stone, M.D.
Deputy Director for Safety
Division of Psychiatry
Office of Neuroscience Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARC B STONE
10/06/2021 03:01:53 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

018936Orig1s111

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 capsules) for oral use
Initial U.S. Approval: 1987

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1).**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).**

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

---------- RECENT MAJOR CHANGES ----------

Warnings and Precautions, Sexual Dysfunction (5.17) 10/2021

---------- INDICATIONS AND USAGE ----------

PROZAC® is a selective serotonin reuptake inhibitor indicated for:
- Acute and maintenance treatment of Major Depressive Disorder (MDD) (1)
- Acute and maintenance treatment of Obsessive Compulsive Disorder (OCD) (1)
- Acute and maintenance treatment of Bulimia Nervosa (1)
- Acute treatment of Panic Disorder, with or without agoraphobia (1)

PROZAC and olanzapine in combination for treatment of:
- Acute Depressive Episodes Associated with Bipolar I Disorder (1)
- Treatment Resistant Depression (1)

----------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)	Oral in combination with olanzapine: 2.5 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)	

- 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)

PROZAC and olanzapine in combination:
- Dosage adjustments 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 in adults (2.5, 2.6)
- Safety of the coadministration of doses above 12 mg olanzapine with 50 mg fluoxetine has not been evaluated in children and adolescents ages 10 to 17 (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

- Pulvules: 10 mg, 20 mg, 40 mg (3)

---------- CONTRAINDICATIONS ----------

- Serotonin Syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with PROZAC or within 5 weeks of stopping treatment with PROZAC. Do not use PROZAC within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start PROZAC in a patient who is being treated with linezolid or intravenous methylene blue (4.1)
- Pimozide: Do not use. Risk of QT prolongation and drug interaction (4.2, 5.11, 7.7, 7.8)
- Thioridazine: Do not use. Risk of QT interval prolongation and elevated thioridazine plasma levels. Do not use thioridazine within 5 weeks of discontinuing PROZAC. Do not use thioridazine within 5 weeks of discontinuing PROZAC (4.2, 5.11, 7.7, 7.8)
- When using PROZAC and olanzapine in combination, also refer to the Contraindications section of the package insert for Symbyax (4)

---------- WARNINGS AND PRECAUTIONS ----------

- *Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults:* Monitor for clinical worsening and suicidal thinking and behavior (5.1)
- *Serotonin Syndrome:* Serotonin syndrome has been reported with SSRIs and SNRIs, including PROZAC, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort). If such symptoms occur, discontinue PROZAC and initiate supportive treatment. If concomitant use of PROZAC with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (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 other drugs that affect coagulation may potentiate the risk of gastrointestinal or other bleeding (5.7)
- *Angle-Closure Glaucoma:* Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5.8)
- *Hyponatremia:* Has been reported with PROZAC in association with syndrome of inappropriate antidiuretic hormone (SIADH). Consider discontinuing if symptomatic hyponatremia occurs (5.9)
- *Anxiety and Insomnia:* May occur (5.10)
- *QT Prolongation:* QT prolongation and ventricular arrhythmia including Torsades de Pointes have been reported with PROZAC use. Use with caution in conditions that predispose to arrhythmias or increased fluoxetine exposure. Use cautiously in patients with risk factors for QT prolongation (4.2, 5.11)
- *Potential for Cognitive and Motor Impairment:* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery (5.13)
- *Long Half-Life:* Changes in dose will not be fully reflected in plasma for several weeks (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 (5.16)
- *Sexual Dysfunction*: PROZAC may cause symptoms of sexual dysfunction (5.17)

---------- 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*

---------- DRUG INTERACTIONS ----------

- *Monoamine Oxidase Inhibitors (MAOIs):* (2.9, 2.10, 4.1, 5.2)
- *Drugs Metabolized by CYP2D6:* Fluoxetine is a potent inhibitor of CYP2D6 enzyme pathway (7.7)
- *Tricyclic Antidepressants (TCAs):* Monitor TCA levels during coadministration with PROZAC or when PROZAC has been recently discontinued (5.2, 7.7)
- *CNS Acting Drugs:* Caution should be used when taken in combination with other centrally acting drugs (7.2)
- *Benzodiazepines:* Diazepam – increased t½, alprazolam - further psychomotor performance decrement due to increased levels (7.7)
- *Antipsychotics:* Potential for elevation of haloperidol and clozapine levels (7.7)
- *Anticonvulsants:* Potential for elevated phenytoin and carbamazepine levels and clinical anticonvulsant toxicity (7.7)
- *Serotonergic Drugs:* (2.9, 2.10, 4.1, 5.2)
- *Drugs that Interfere with Hemostasis (e.g. NSAIDs, Aspirin, Warfarin):* May potentiate the risk of bleeding (7.4)
- *Drugs Tightly Bound to Plasma Proteins:* May cause a shift in plasma concentrations (7.6, 7.7)
- *Olanzapine:* When used in combination with PROZAC, also refer to the Drug Interactions section of the package insert for Symbyax (7.7)
- *Drugs that Prolong the QT Interval:* Do not use Prozac with thioridazine or pimozide. Use with caution in combination with other drugs that prolong the QT interval (4.2, 5.11, 7.7, 7.8)

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

- *Pregnancy:* SSRI use, particularly later in pregnancy, may increase risk for persistent pulmonary hypertension and symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, tremor, irritability) in the neonate (8.1)
- *Pediatric Use*: Safety and effectiveness of PROZAC in patients <8 years of age with Major Depressive Disorder and <7 years of age with OCD have not been established. Safety and effectiveness of PROZAC and olanzapine in combination in patients <10 years of age for depressive episodes associated with Bipolar I Disorder have not been established (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 Medication Guide.

Revised: 10/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION
- 2.1 Major Depressive Disorder
- 2.2 Obsessive Compulsive Disorder
- 2.3 Bulimia Nervosa
- 2.4 Panic Disorder
- 2.5 PROZAC and Olanzapine in Combination: Depressive Episodes Associated with Bipolar I Disorder
- 2.6 PROZAC and Olanzapine in Combination: Treatment Resistant Depression
- 2.7 Dosing in Specific Populations
- 2.8 Discontinuation of Treatment
- 2.9 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders
- 2.10 Use of PROZAC with Other MAOIs such as Linezolid or Methylene Blue

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS
- 4.1 Monoamine Oxidase Inhibitors (MAOIs)
- 4.2 Other Contraindications

5 WARNINGS AND PRECAUTIONS
- 5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults
- 5.2 Serotonin Syndrome
- 5.3 Allergic Reactions and Rash
- 5.4 Screening Patients for Bipolar Disorder and Monitoring for Mania/Hypomania
- 5.5 Seizures
- 5.6 Altered Appetite and Weight
- 5.7 Abnormal Bleeding
- 5.8 Angle-Closure Glaucoma
- 5.9 Hyponatremia
- 5.10 Anxiety and Insomnia
- 5.11 QT Prolongation
- 5.12 Use in Patients with Concomitant Illness
- 5.13 Potential for Cognitive and Motor Impairment
- 5.14 Long Elimination Half-Life
- 5.15 Discontinuation Adverse Reactions
- 5.16 PROZAC and Olanzapine in Combination
- 5.17 Sexual Dysfunction

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS
- 7.1 Monoamine Oxidase Inhibitors (MAOI)
- 7.2 CNS Acting Drugs
- 7.3 Serotonergic Drugs
- 7.4 Drugs that Interfere with Hemostasis (e.g., NSAIDS, Aspirin, Warfarin)
- 7.5 Electroconvulsive Therapy (ECT)
- 7.6 Potential for Other Drugs to affect PROZAC
- 7.7 Potential for PROZAC to affect Other Drugs
- 7.8 Drugs that Prolong the QT Interval

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

9 DRUG ABUSE AND DEPENDENCE
- 9.3 Dependence

10 OVERDOSAGE
- 10.1 Human Experience
- 10.2 Animal Experience
- 10.3 Management of Overdose

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Specific Populations

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
- 14.1 Major Depressive Disorder
- 14.2 Obsessive Compulsive Disorder
- 14.3 Bulimia Nervosa
- 14.4 Panic Disorder

16 HOW SUPPLIED/STORAGE AND HANDLING
- 16.1 How Supplied
- 16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

- **Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.1)].***
- **In patients of all ages who are started on antidepressant therapy, monitor closely for worsening and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.1)].***
- **PROZAC is not approved for use in children less than 7 years of age *[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

PROZAC® is indicated for the treatment of:

- Acute and maintenance treatment of Major Depressive Disorder *[see Clinical Studies (14.1)]*.
- Acute and maintenance treatment of obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD) *[see Clinical Studies (14.2)].*
- Acute and maintenance treatment of binge-eating and vomiting behaviors in patients with moderate to severe Bulimia Nervosa *[see Clinical Studies (14.3)]*.
- Acute treatment of Panic Disorder, with or without agoraphobia *[see Clinical Studies (14.4)].*

PROZAC and Olanzapine in Combination is indicated for the treatment of:

- Acute treatment of depressive episodes associated with Bipolar I Disorder.
- Treatment resistant depression (Major Depressive Disorder in 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 depressive episodes associated with Bipolar I Disorder or the treatment of treatment resistant depression.

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

2 DOSAGE AND ADMINISTRATION

2.1 Major Depressive Disorder

Initial Treatment

Adult — Initiate PROZAC 20 mg/day orally in the morning. Consider a dose increase after several weeks if insufficient clinical improvement is observed. Administer doses above 20 mg/day once daily in the morning or twice daily (i.e., morning and noon).The maximum fluoxetine dose should not exceed 80 mg/day.

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 *[see Clinical Studies (14.1)]*.

Pediatric (children and adolescents) — Initiate PROZAC 10 or 20 mg/day. After 1 week at 10 mg/day, increase the dose 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. Consider a dose increase to 20 mg/day after several weeks if insufficient clinical improvement is observed. 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)]*.

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.

Periodically reassess to determine the need for maintenance treatment.

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 Warnings and Precautions (5.2) and Drug Interactions (7.7)]*.

2.2 Obsessive Compulsive Disorder

Initial Treatment

Adult — Initiate PROZAC 20 mg/day, orally in the morning. Consider a dose increase after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer. Administer doses above 20 mg/day once daily in the morning or twice daily (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.

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.

Pediatric (children and adolescents) — In adolescents and higher weight children, initiate treatment with a dose of 10 mg/day. After 2 weeks, increase the dose to 20 mg/day. Consider additional dose increases 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, initiate treatment with a dose of 10 mg/day. Consider additional dose increases 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.

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)]*.

Periodically reassess to determine the need for treatment.

2.3 Bulimia Nervosa

Initial Treatment — Administer PROZAC 60 mg/day 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. 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.

Periodically reassess to determine the need for maintenance treatment.

2.4 Panic Disorder

Initial Treatment — Initiate treatment with PROZAC 10 mg/day. After one week, increase the dose to 20 mg/day. Consider a dose increase 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. 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)]*. The most frequently administered dose in the 2 flexible-dose clinical trials was 20 mg/day.

Periodically reassess 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.

Adult — Administer fluoxetine 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. Make dosage adjustments, if indicated, 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 of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies. Periodically re-examine the need for continued pharmacotherapy.

Children and adolescents (10 -17 years of age) — Administer olanzapine and fluoxetine combination once daily in the evening, generally beginning with 2.5 mg of olanzapine and 20 mg of fluoxetine. Make dosage adjustments, if indicated, according to efficacy and tolerability. Safety of co-administration of doses above 12 mg of olanzapine with 50 mg of fluoxetine has not been evaluated in pediatric clinical studies. Periodically re-examine the need for continued pharmacotherapy.

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. Adjust dosage, if indicated, with the individual components according to efficacy and tolerability.

Table 1: Approximate Dose Correspondence Between Symbyax[1] 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

[1] Symbyax (olanzapine/fluoxetine HCL) is a fixed-dose combination of PROZAC and olanzapine.

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.

Administer fluoxetine 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. Adjust dosage, if indicated, 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. Adjust dosage, if indicated, with the individual components according to efficacy and tolerability.

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

Geriatric — Consider a lower or less frequent dosage for the elderly *[see Use in Specific Populations (8.5)]*.

Hepatic Impairment — As with many other medications, use a lower or less frequent dosage 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 (5.12)]*.

PROZAC and Olanzapine in Combination — Use a starting dose of oral olanzapine 2.5 to 5 mg with fluoxetine 20 mg 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. Titrate slowly and adjust dosage as needed in patients who exhibit a combination of factors that may slow metabolism. PROZAC and olanzapine in combination have not been systematically studied in patients over 65 years of age or in patients less than 10 years of age *[see Warnings and Precautions (5.16) and Drug Interactions (7.7)]*.

2.8 Discontinuation of Treatment

Symptoms associated with discontinuation of fluoxetine, SNRIs, and SSRIs, have been reported *[see Warnings and Precautions (5.15)]*.

2.9 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with PROZAC. Conversely, at least 5 weeks should be allowed after stopping PROZAC before starting an MAOI intended to treat psychiatric disorders *[see Contraindications (4.1)]*.

2.10 Use of PROZAC with Other MAOIs such as Linezolid or Methylene Blue

Do not start PROZAC in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered *[see Contraindications (4.1)]*.

In some cases, a patient already receiving PROZAC therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks

of serotonin syndrome in a particular patient, PROZAC should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for five weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with PROZAC may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue *[see Warnings and Precautions (5.2)]*.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with PROZAC is unclear. The healthcare provider should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use *[see Warnings and Precautions (5.2)]*.

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

4 CONTRAINDICATIONS

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

4.1 Monoamine Oxidase Inhibitors (MAOIs)

The use of MAOIs intended to treat psychiatric disorders with PROZAC or within 5 weeks of stopping treatment with PROZAC is contraindicated because of an increased risk of serotonin syndrome. The use of PROZAC within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Dosage and Administration (2.9) and Warnings and Precautions (5.2)]*.

Starting PROZAC in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Dosage and Administration (2.10) and Warnings and Precautions (5.2)]*.

4.2 Other Contraindications

The use of PROZAC is contraindicated with the following:

- Pimozide *[see Warnings and Precautions (5.11) and Drug Interactions (7.7, 7.8)]*
- Thioridazine *[see Warnings and Precautions (5.11) and Drug Interactions (7.7, 7.8)]*

Pimozide and thioridazine prolong the QT interval. PROZAC can increase the levels of pimozide and thioridazine through inhibition of CYP2D6. PROZAC can also prolong the QT interval.

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 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

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 (5.15)]*.

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 for Major Depressive Disorder and Obsessive Compulsive Disorder; and PROZAC in combination with olanzapine for the acute treatment of depressive episodes associated with Bipolar I Disorder.

5.2 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including PROZAC, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of PROZAC with MAOIs intended to treat psychiatric disorders is contraindicated. PROZAC should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking PROZAC. PROZAC should be discontinued before initiating treatment with the MAOI *[see Contraindications (4.1) and Dosage and Administration (2.9, 2.10)]*.

If concomitant use of PROZAC with other serotonergic drugs, i.e., triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, amphetamines, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with PROZAC and any concomitant serotonergic agents, should be discontinued immediately if the above events 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 (7.4)]*.

5.8 Angle-Closure Glaucoma

Angle-Closure Glaucoma — The pupillary dilation that occurs following use of many antidepressant drugs including Prozac may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.9 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.

5.10 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]*.

5.11 QT Prolongation

Post-marketing cases of QT interval prolongation and ventricular arrhythmia including Torsades de Pointes have been reported in patients treated with PROZAC. PROZAC should be used with caution in patients with congenital long QT syndrome; a previous history of QT prolongation; a family history of long QT syndrome or sudden cardiac death; and other conditions that predispose to QT prolongation and ventricular arrhythmia. Such conditions include concomitant use of drugs that prolong the QT interval; hypokalemia or hypomagnesemia; recent myocardial infarction, uncompensated heart failure, bradyarrhythmias, and other significant arrhythmias; and conditions that predispose to increased fluoxetine exposure (overdose, hepatic impairment, use of CYP2D6 inhibitors, CYP2D6 poor metabolizer status, or use of other highly protein-bound drugs). PROZAC is primarily metabolized by CYP2D6 *[see Contraindications (4.2), Adverse Reactions (6.2), Drug Interactions (7.7, 7.8), Overdosage (10.1), and Clinical Pharmacology (12.3)]*.

Pimozide and thioridazine are contraindicated for use with PROZAC. Avoid the concomitant use of drugs known to prolong the QT interval. These include specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, mesoridazine, droperidol,); specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin); Class 1A antiarrhythmic medications (e.g., quinidine, procainamide); Class III antiarrhythmics (e.g., amiodarone, sotalol); and

others (e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol or tacrolimus) *[see Drug Interactions (7.7, 7.8) and Clinical Pharmacology (12.3)]*.

Consider ECG assessment and periodic ECG monitoring if initiating treatment with PROZAC in patients with risk factors for QT prolongation and ventricular arrhythmia. Consider discontinuing PROZAC and obtaining a cardiac evaluation if patients develop signs or symptoms consistent with ventricular arrhythmia.

5.12 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.

5.13 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.

5.14 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)]*.

5.15 Discontinuation Adverse Reactions

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 healthcare provider 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.

5.16 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.

5.17 Sexual Dysfunction

Use of SSRIs, including PROZAC, may cause symptoms of sexual dysfunction *[see Adverse Reactions (6.1)]*. In male patients, SSRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SSRI use may result in decreased libido and delayed or absent orgasm.

It is important for prescribers to inquire about sexual function prior to initiation of PROZAC and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*
- Allergic Reactions and Rash *[see Warnings and Precautions (5.3)]*
- Screening Patients for Bipolar Disorder and Monitoring for Mania/Hypomania *[see Warnings and Precautions (5.4)]*
- Seizures *[see Warnings and Precautions (5.5)]*
- Altered Appetite and Weight *[see Warnings and Precautions (5.6)]*

- Abnormal Bleeding *[see Warnings and Precautions (5.7)]*
- Angle-Closure Glaucoma *[see Warnings and Precautions (5.8)]*
- Hyponatremia *[see Warnings and Precautions (5.9)]*
- Anxiety and Insomnia *[see Warnings and Precautions (5.10)]*
- QT Prolongation *[see Warnings and Precautions (5.11)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.13)]*
- Discontinuation Adverse Reactions *[see Warnings and Precautions (5.15)]*
- Sexual Dysfunction *[see Warnings and Precautions (5.17)]*

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. 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.

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[1,2]

	Percentage of Patients Reporting Event							
	Major Depressive Disorder		**OCD**		**Bulimia**		**Panic Disorder**	
Body System/ Adverse Reaction	**PROZAC** (N=1728)	**Placebo** (N=975)	**PROZAC** (N=266)	**Placebo** (N=89)	**PROZAC** (N=450)	**Placebo** (N=267)	**PROZAC** (N=425)	**Placebo** (N=342)
Body as a Whole								
Asthenia	9	5	15	11	21	9	7	7
Flu syndrome	3	4	10	7	8	3	5	5
Cardiovascular System								
Vasodilatation	3	2	5	--	2	1	1	--
Digestive System								
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
Nervous System								
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
Respiratory System								

Pharyngitis	3	3	11	9	10	5	3	3
Sinusitis	1	4	5	2	6	4	2	3
Yawn	--	--	7	--	11	--	1	--
Skin and Appendages								
Sweating	8	3	7	--	8	3	2	2
Rash	4	3	6	3	4	4	2	2
Urogenital System								
Impotence[3]	2	--	--	--	7	--	1	--
Abnormal ejaculation[3]	--	--	7	--	7	--	2	1

[1] Incidence less than 1%.

[2] Includes US data for Major Depressive Disorder, OCD, Bulimia, and Panic Disorder clinical trials, plus non-US data for Panic Disorder clinical trials.

[3] 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[1,2]

	Percentage of Patients Reporting Event	
	Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined	
Body System/ Adverse Reaction	**PROZAC** (N=2869)	**Placebo** (N=1673)
Body as a Whole		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	2	1
Digestive System		
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
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
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
Respiratory System		
Yawn	3	--
Skin and Appendages		
Sweating	7	3
Rash	4	3
Pruritus	3	2

Special Senses		
Abnormal vision	2	1

[1] Incidence less than 1%.

[2] 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[1]

Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined (N=1533)	**Major Depressive Disorder** (N=392)	**OCD** (N=266)	**Bulimia** (N=450)	**Panic Disorder** (N=425)
Anxiety (1%)	--	Anxiety (2%)	--	Anxiety (2%)
--	--	--	Insomnia (2%)	--
--	Nervousness (1%)	--	--	Nervousness (1%)
--	--	Rash (1%)	--	--

[1] 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.

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 healthcare providers 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.

Symptoms of sexual dysfunction occasionally persist after discontinuation of 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, healthcare providers should routinely inquire about such possible side effects.

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[1].

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.

Investigations — *Frequent:* QT interval prolongation (QT_cF ≥450 msec)[3].

Nervous System — *Frequent:* emotional lability; *Infrequent:* akathisia, ataxia, balance disorder[1], bruxism[1], 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[2].

[1] MedDRA dictionary term from integrated database of placebo controlled trials of 15870 patients, of which 9673 patients received fluoxetine.

[2] 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.

[3] QT prolongation data are based on routine ECG measurements in clinical trials.

6.2 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 not always possible 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[1], cataract, cerebrovascular accident[1], 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[1], epidermal necrolysis, erythema multiforme, erythema nodosum, exfoliative dermatitis, galactorrhea, gynecomastia, heart arrest[1], hepatic failure/necrosis, hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure, memory impairment, movement disorders developing in patients with risk factors including drugs associated with such reactions and worsening of pre-existing movement disorders, optic neuritis, pancreatitis[1], pancytopenia, pulmonary embolism, pulmonary hypertension, QT prolongation, Stevens-Johnson syndrome, thrombocytopenia[1], thrombocytopenic purpura, ventricular tachycardia (including Torsades de Pointes–type arrhythmias), vaginal bleeding, and violent behaviors[1].

[1] 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)

[See Dosage and Administration (2.9, 2.10), Contraindications (4.1), and Warnings and Precautions (5.2)].

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

[See Dosage and Administration (2.9, 2.10), Contraindications (4.1), and Warnings and Precautions (5.2)].

7.4 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)]*.

7.5 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.

7.6 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)]*.

7.7 Potential for PROZAC to affect Other Drugs

Pimozide — Concomitant use in patients taking pimozide is contraindicated. Pimozide can prolong the QT interval. Fluoxetine can increase the level of pimozide through inhibition of CYP2D6. Fluoxetine can also prolong the QT interval. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QT prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT prolongation warrants restricting the concurrent use of pimozide and PROZAC *[see Contraindications (4.2), Warnings and Precautions (5.11), and Drug Interactions (7.8)]*.

Thioridazine — Thioridazine should not be administered with PROZAC or within a minimum of 5 weeks after PROZAC has been discontinued, because of the risk of QT Prolongation *[see Contraindications (4.2), Warnings and Precautions (5.11), and Drug Interactions (7.8)]*.

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_{max} 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 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 (4.2)]*.

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 Warnings and Precautions (5.2) and 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.

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 *[see Warnings and Precautions (5.2)]*.

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.

7.8 Drugs that Prolong the QT Interval

Do not use PROZAC in combination with thioridazine or pimozide. Use PROZAC with caution in combination with other drugs that cause QT prolongation. These include: specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, mesoridazine, droperidol); specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin); Class 1A antiarrhythmic medications (e.g., quinidine, procainamide); Class III antiarrhythmics (e.g., amiodarone, sotalol); and others (e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol or tacrolimus). PROZAC is primarily metabolized by CYP2D6. Concomitant treatment with CYP2D6 inhibitors can increase the concentration of PROZAC. Concomitant use of other highly protein-bound drugs can increase the concentration of *PROZAC [see Contraindications (4.2), Warnings and Precautions (5.11), Drug Interactions (7.7), and Clinical Pharmacology (12.3)]*.

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 Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/.

Risk Summary

Available data from published epidemiologic studies and postmarketing reports over several decades have not established an increased risk of major birth defects or miscarriage. Some studies have reported an increased incidence of cardiovascular malformations; however, these studies results do not establish a causal relationship *(see Data)*. There are risks associated with untreated depression in pregnancy and risks of persistent pulmonary hypertension of the newborn (PPHN) *(see Data)* and poor neonatal adaptation with exposure to selective serotonin reuptake inhibitors (SSRIs), including PROZAC, during pregnancy *(see Clinical Considerations).*

In rats and rabbits treated with fluoxetine during the period of organogenesis, there was no evidence of developmental effects at doses up to 1.6 and 3.9 times, respectively, the maximum recommended human dose (MRHD) of 60 mg/day given to adolescents on a mg/m^2 basis. However, in other reproductive studies in rats, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths early after birth occurred at doses that are 1.5 times (during gestation) and 0.97 time (during gestation and lactation) the MRHD given to adolescents on a mg/m^2 basis.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Women who discontinue antidepressants during pregnancy are more likely to experience a relapse of major depression than women who continue antidepressants. This finding is from a prospective, longitudinal study that followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Fetal/Neonatal adverse reactions

Neonates exposed to PROZAC and other SSRI or SNRIs 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, tremors, jitteriness, irritability, and constant crying. These findings are consistent with either a direct toxic effect of SSRIs and SNRIs or possibly a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions (5.2)]*.

Data

Human Data — It has been shown that SSRIs (including fluoxetine) can cross the placenta. Published epidemiological studies of pregnant women exposed to fluoxetine have not established an increased risk of major birth defects, miscarriage, and other adverse developmental outcomes. Several publications reported an increased incidence of cardiovascular malformations in children with in utero exposure to fluoxetine. However, these studies results do not establish a causal relationship. Methodologic limitations of these observational studies include possible exposure and outcome misclassification, lack of adequate controls, adjustment for confounders and confirmatory studies. However, these studies cannot definitely establish or exclude any drug-associated risk during pregnancy.

Exposure to SSRIs, particularly later in pregnancy, may have an increased risk for PPHN. PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality.

Animal Data — In embryofetal development studies in rats and rabbits, there was no evidence of malformations or developmental variations following administration of fluoxetine at doses up to 12.5 and 15 mg/kg/day, respectively (1.6 and 3.9 times, respectively, the MRHD of 60 mg given to adolescents on a mg/m^2 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 given to adolescents on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.97 time the MRHD given to adolescents on a mg/m^2 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 (0.65 time the MRHD given to adolescents on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Data from published literature report the presence of fluoxetine and norfluoxetine in human milk *(see Data).* There are reports of agitation, irritability, poor feeding, and poor weight gain in infants exposed to fluoxetine through breast milk *(see Clinical Considerations).* There are no data on the effect of fluoxetine or its metabolites on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PROZAC and any potential adverse effects on the breastfed child from PROZAC or the underlying maternal condition.

Clinical Considerations

Infants exposed to PROZAC should be monitored for agitation, irritability, poor feeding, and poor weight gain.

Data

A study of 19 nursing mothers on fluoxetine with daily doses of 10-60 mg showed that fluoxetine was detectable in 30% of nursing infant sera (range: 1 to 84 ng/mL) whereas norfluoxetine was found in 85% (range: <1 to 265 ng/mL).

8.4 Pediatric Use

Use of PROZAC in children — 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 ≤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 ≤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.

Animal Data — Significant toxicity on muscle tissue, neurobehavior, reproductive organs, and bone development has been observed following exposure of juvenile rats to fluoxetine from weaning through maturity. Oral administration of fluoxetine to rats from weaning postnatal day 21 through adulthood day 90 at 3, 10, or 30 mg/kg/day was associated with testicular degeneration and necrosis, epididymal vacuolation and hypospermia (at 30 mg/kg/day corresponding to plasma exposures [AUC] approximately 5-10 times the average AUC in pediatric patients at the MRHD of 20 mg/day), increased serum levels of creatine kinase (at AUC as low as 1-2 times the average AUC in pediatric patients at the MRHD of 20 mg/day), skeletal muscle degeneration and necrosis, decreased femur length/growth and body weight gain (at AUC 5-10 times the average AUC in pediatric patients at the MRHD of 20 mg/day). The high dose of 30 mg/kg/day exceeded a maximum tolerated dose. When animals were evaluated after a drug-free period (up to 11 weeks after cessation of dosing), fluoxetine was associated with neurobehavioral abnormalities (decreased reactivity at AUC as low as approximately 0.1-0.2 times the average AUC in pediatric patients at the MRHD and learning deficit at the high dose), and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose). In addition, the testicular and epididymal microscopic lesions and decreased sperm concentrations found in high dose group were also observed, indicating that the drug effects on reproductive organs are irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed.

These fluoxetine toxicities in juvenile rats have not been observed in adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving 3, 10, or 30 mg/kg/day doses in this study are approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in pediatric patients receiving the MRHD of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, are approximately 0.3-0.8, 1-8, and 3-20 times, respectively, the pediatric exposure at the MRHD.

A specific effect on bone development was reported in juvenile mice administered fluoxetine by the intraperitoneal route to 4 week old mice for 4 weeks at doses 0.5 and 2 times the oral MRHD of 20 mg/day on mg/m^2 basis. There was a decrease in bone mineralization and density at both doses, but the overall growth (body weight gain or femur length) was not affected.

Use of PROZAC in combination with olanzapine in children and adolescents: Safety and efficacy of PROZAC and olanzapine in combination in patients 10 to 17 years of age have been established for the acute treatment of depressive episodes associated with Bipolar I Disorder. Safety and effectiveness of PROZAC and olanzapine in combination in patients less than 10 years of age have not been established.

8.5 Geriatric Use

US fluoxetine clinical trials included 687 patients ≥65 years of age and 93 patients ≥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 (5.9)]*.

Clinical studies of olanzapine and fluoxetine in combination did not include sufficient numbers of patients ≥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, healthcare providers 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

The following have been reported with fluoxetine overdosage:

- Seizures, which may be delayed, and altered mental status including coma.
- Cardiovascular toxicity, which may be delayed, including QRS and QTc interval prolongation, wide complex tachyarrhythmias, torsade de pointes, and cardiac arrest. Hypertension most commonly seen, but rarely can see hypotension alone or with co-ingestants including alcohol.

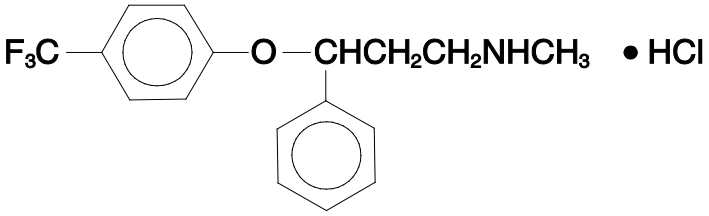
- Serotonin syndrome (patients with a multiple drug overdosage with other pro-serotonergic drugs may have a higher risk).

Gastrointestinal decontamination with activated charcoal should be considered in patients who present early after a fluoxetine overdose.

Consider contacting a Poison Center (1-800-221-2222) or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

PROZAC® (fluoxetine capsules, USP) is a selective serotonin reuptake inhibitor for oral administration. It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO$•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® 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.

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_1-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.

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.

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 α_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 (7.7)]*.

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 (5.14)]*. 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.

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) and 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 ± 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 2.4 and 1.44 times, respectively, the maximum recommended human dose (MRHD) of 20 mg given to children on a mg/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 0.97 and 1.6 times, respectively, the MRHD of 60 mg given to adolescents on a mg/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

Efficacy for PROZAC was established for the:

- Acute and maintenance treatment of Major Depressive Disorder in adults, and children and adolescents (8 to 18 years) in 7 short-term and 2 long-term, placebo-controlled trials *[see Clinical Studies 14.1].*
- Acute treatment of obsessions and compulsions in adults, and children and adolescents (7 to 17 years) with Obsessive Compulsive Disorder (OCD) in 3 short-term placebo-controlled trials *[see Clinical Studies (14.2)].*
- Acute and maintenance treatment of binge-eating and vomiting behaviors in adult patients with moderate to severe Bulimia Nervosa in 3 short-term and 1 long-term, placebo-controlled trials *[see Clinical Studies (14.3)]*.
- Acute treatment of Panic Disorder, with or without agoraphobia, in adult patients in 2 short-term, placebo-controlled trials *[see Clinical Studies (14.4)]*.

Efficacy for PROZAC and olanzapine in combination was established for the:

- Acute treatment of depressive episodes in Bipolar I Disorder in adults, and children and adolescents (10 to 17 years) in 3 short-term, placebo-controlled trials.
- Acute and maintenance treatment of treatment resistant depression in adults (18 to 85 years) in 3 short-term, placebo-controlled trials and 1 randomized withdrawal study with an active control.

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%).

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 ≤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.

Maintenance Treatment

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 ≥14 for 3 weeks) was observed for patients taking PROZAC compared with those on placebo.

An additional maintenance 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 ≤9, a CGI-Severity rating of ≤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 fluoxetine delayed-release capsules 90 mg once weekly, PROZAC 20 mg once daily, or placebo. 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.

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

		PROZAC		
Outcome Classification	Placebo	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 healthcare provider 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 10 mg, 20 mg and 40 mg capsule strengths and packages as follows:

	Pulvule Strength		
	10 mg[1]	**20 mg[1]**	**40 mg[1]**
Pulvule No.[2]	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
NDC Codes:			
Bottles of 30		0777-3105-30	0777-3107-30
Bottles 100	0777-3104-02	0777-3105-02	
Bottles of 2000		0777-3105-07	

[1] Fluoxetine base equivalent.

[2] 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

Advise the patient to read the FDA-approved patient labeling (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.

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.

Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

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)]*.

Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of PROZAC and other serotonergic agents including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort *[see Contraindications (4.1), Warnings and Precautions (5.2), and Drug Interactions (7.3)]*.

Patients should be advised of the signs and symptoms associated with serotonin syndrome that may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be cautioned to seek medical care immediately if they experience these symptoms.

Allergic Reactions and Rash

Patients should be advised to notify their healthcare provider 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.

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 (7.4)]*. Patients should be advised to call their healthcare provider if they experience any increased or unusual bruising or bleeding while taking PROZAC.

Angle-Closure Glaucoma

Patients should be advised that taking Prozac can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible *[see Warnings and Precautions (5.8)]*.

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 (5.9)]*.

QT Prolongation

Patients should be advised that QT interval prolongation and ventricular arrhythmia including Torsades de Pointes have been reported in patients treated with PROZAC. Signs and symptoms of ventricular arrhythmia include fast, slow, or irregular heart rate, dyspnea, syncope, or dizziness, which may indicate serious cardiac arrhythmia *[see Warnings and Precautions (5.11)]*.

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 (5.13)].*

Use of Concomitant Medications

Patients should be advised to inform their healthcare provider 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 healthcare providers if they plan to discontinue any medications they are taking while on PROZAC.

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 healthcare provider *[see Warnings and Precautions (5.15)]*. Patients should be advised to consult with their healthcare provider if their symptoms do not improve with PROZAC.

Sexual Dysfunction

Advise patients that use of PROZAC may cause symptoms of sexual dysfunction in both male and female patients. Inform patients that they should discuss any changes in sexual function and potential management strategies with their healthcare provider *[see Warnings and Precautions (5.17)]*.

Use in Specific Populations

Pregnancy — Advise pregnant women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with PROZAC.

Advise patients that PROZAC use later in pregnancy may lead to increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN) *[see Use in Specific Populations (8.1)]*.

Advise women that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PROZAC during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation —Advise breastfeeding women using PROZAC to monitor infants for agitation, irritability, poor feeding and poor weight gain and to seek medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Pediatric Use of PROZAC — 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 *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.4)]*.

Pediatric Use of PROZAC and olanzapine in combination - Safety and efficacy of PROZAC and olanzapine in combination in patients 10 to 17 years of age have been established for the acute treatment of depressive episodes associated with Bipolar I Disorder *[see Warnings and Precautions (5.16) and Use in Specific Populations (8.4)]*.

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA

A3.0-PRZ-0006-USPI-20211006

Medication Guide

PROZAC® (PRO-zac)
(fluoxetine capsules)
for oral use

Read the Medication Guide that comes with PROZAC before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk with your healthcare provider if there is something you do not understand or want to learn more about.

What is the most important information I should know about PROZAC?

PROZAC and other antidepressant medicines may cause serious side effects, including:

1. Suicidal thoughts or actions:

- **PROZAC and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment or when the dose is changed.**
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
  - New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
  - Pay particular attention to such changes when PROZAC is started or when the dose is changed.

Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety or panic attacks
- feeling agitated, restless, angry or irritable
- trouble sleeping

- an increase in activity or talking more than what is normal for you
- other unusual changes in behavior or mood

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency. PROZAC may be associated with these serious side effects:

2. **Serotonin Syndrome. This condition can be life-threatening and may include:**

- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- racing heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle rigidity
- dizziness
- flushing
- tremor
- seizures

3. **Severe allergic reactions:**

- trouble breathing
- swelling of the face, tongue, eyes or mouth
- rash, itchy welts (hives) or blisters, alone or with fever or joint pain

4. **Abnormal bleeding:** PROZAC and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.

5. **Visual problems:**

- eye pain
- changes in vision
- swelling or redness in or around the eye

Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

6. **Seizures or convulsions**

7. **Manic episodes:**

- greatly increased energy
- severe trouble sleeping
- racing thoughts

- reckless behavior
- unusually grand ideas
- excessive happiness or irritability
- talking more or faster than usual

8. **Changes in appetite or weight.** Children and adolescents should have height and weight monitored during treatment.

9. **Low salt (sodium) levels in the blood.** Elderly people may be at greater risk for this. Symptoms may include:

   - headache
   - weakness or feeling unsteady
   - confusion, problems concentrating or thinking or memory problems

10. **Changes in the electrical activity of your heart (QT prolongation and ventricular arrhythmia including Torsades de Pointes). This condition can be life threatening. The symptoms may include:**

    - fast, slow, or irregular heartbeat
    - shortness of breath
    - dizziness or fainting

11. **Sexual problems (dysfunction).** Taking selective serotonin reuptake inhibitors (SSRIs), including PROZAC, may cause sexual problems.
    - Symptoms in males may include:
      - Delayed ejaculation or inability to have an ejaculation
      - Decreased sex drive
      - Problems getting or keeping an erection
    - Symptoms in females may include:
      - Decreased sex drive
      - Delayed orgasm or inability to have an orgasm

    Talk to your healthcare provider if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with PROZAC. There may be treatments your healthcare provider can suggest.

Do not stop PROZAC without first talking to your healthcare provider. Stopping PROZAC too quickly may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless or changes in sleep habits
- headache, sweating, nausea, dizziness
- electric shock-like sensations, shaking, confusion

What is PROZAC?

PROZAC is a prescription medicine used to treat depression. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider.

PROZAC is used to treat:

- Major Depressive Disorder (MDD)
- Obsessive Compulsive Disorder (OCD)
- Bulimia Nervosa*
- Panic Disorder*
- Depressive episodes associated with Bipolar I Disorder, taken with olanzapine (Zyprexa)
- Treatment Resistant Depression (depression that has not gotten better with at least 2 other treatments), taken with olanzapine (Zyprexa)*

*Not approved for use in children

Talk to your healthcare provider if you do not think that your condition is getting better with PROZAC treatment.

Who should not take PROZAC?

Do not take PROZAC if you:

- are allergic to fluoxetine hydrochloride or any of the ingredients in PROZAC. See the end of this Medication Guide for a complete list of ingredients in PROZAC.
- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
  - Do not take an MAOI within 5 weeks of stopping PROZAC unless directed to do so by your physician.
  - Do not start PROZAC if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.

  People who take PROZAC close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:

  - high fever
  - uncontrolled muscle spasms
  - stiff muscles
  - rapid changes in heart rate or blood pressure
  - confusion
  - loss of consciousness (pass out)
- **take Mellaril® (thioridazine). Do not take Mellaril® within 5 weeks of stopping PROZAC because this can cause serious heart rhythm problems or sudden death.**
- **take the antipsychotic medicine pimozide (Orap®) because this can cause serious heart problems.**

What should I tell my healthcare provider before taking PROZAC? Ask if you are not sure.

Before starting PROZAC, tell your healthcare provider if you:

- Are taking certain drugs or treatments such as:
  - Triptans used to treat migraine headache
  - Medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, buspirone, SSRIs, SNRIs, MAOIs or antipsychotics
  - Amphetamines
  - Tramadol and fentanyl
  - Over-the-counter supplements such as tryptophan or St. John's Wort
  - Electroconvulsive therapy (ECT)
- have liver problems
- have kidney problems
- have heart problems
- have or had seizures or convulsions
- have bipolar disorder or mania
- have low sodium levels in your blood
- have a history of a stroke
- have high blood pressure
- have or had bleeding problems
- are pregnant or plan to become pregnant. Taking PROZAC late in pregnancy may lead to an increased risk of certain problems in your newborn. Talk to your healthcare provider about the benefits and risks of treating depression during pregnancy.
  - If you become pregnant while taking PROZAC, talk to your healthcare provider about registering with the National Pregnancy Registry for Antidepressants. You can register by calling 1-844-405-6185 or go to https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/.
- are breast-feeding or plan to breast-feed. PROZAC may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if taking PROZAC.

Tell your healthcare provider about all the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. PROZAC and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take PROZAC with your other medicines. Do not start or stop any medicine while taking PROZAC without talking to your healthcare provider first.

If you take PROZAC, you should not take any other medicines that contain fluoxetine hydrochloride including:

- Symbyax
- Sarafem

How should I take PROZAC?

- Take PROZAC exactly as prescribed. Your healthcare provider may need to change the dose of PROZAC until it is the right dose for you.
- PROZAC may be taken with or without food.
- If you miss a dose of PROZAC, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of PROZAC at the same time.
- If you take too much PROZAC, call your healthcare provider or poison control center right away, or get emergency treatment.

What should I avoid while taking PROZAC?

PROZAC can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how PROZAC affects you. Do not drink alcohol while using PROZAC.

What are the possible side effects of PROZAC?

PROZAC may cause serious side effects, including:

- See “What is the most important information I should know about PROZAC?”
- **Problems with blood sugar control.** People who have diabetes and take PROZAC may have problems with low blood sugar while taking PROZAC. High blood sugar can happen when PROZAC is stopped. Your healthcare provider may need to change the dose of your diabetes medicines when you start or stop taking PROZAC.
- **Feeling anxious or trouble sleeping**

Common possible side effects in people who take PROZAC include:

- unusual dreams
- sexual problems
- loss of appetite, diarrhea, indigestion, nausea or vomiting, weakness, or dry mouth
- flu symptoms
- feeling tired or fatigued
- change in sleep habits
- yawning

- sinus infection or sore throat
- tremor or shaking
- sweating
- feeling anxious or nervous
- hot flashes
- rash

Other side effects in children and adolescents include:

- increased thirst
- abnormal increase in muscle movement or agitation
- nose bleed
- urinating more often
- heavy menstrual periods
- possible slowed growth rate and weight change. Your child's height and weight should be monitored during treatment with PROZAC.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of PROZAC. For more information, ask your healthcare provider or pharmacist.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088.

How should I store PROZAC?

- Store PROZAC at room temperature between 59°F and 86°F (15°C to 30°C).
- Keep PROZAC away from light.
- Keep PROZAC bottle closed tightly.

Keep PROZAC and all medicines out of the reach of children.

General information about PROZAC

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PROZAC for a condition for which it was not prescribed. Do not give PROZAC to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about PROZAC. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about PROZAC that is written for healthcare professionals.

For more information about PROZAC call 1-800-Lilly-Rx (1-800-545-5979).

What are the ingredients in PROZAC?

Active ingredient: fluoxetine hydrochloride

Inactive ingredients:

- **PROZAC pulvules:** 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 Pulvules also contains FD&C Blue No. 1 and FD&C Yellow No. 6.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide revised October, 2021

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA

A2.0-PRZ-0004-MG-20211006

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARC B STONE
10/06/2021 03:01:53 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

018936Orig1s111

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
LABELING REVIEW

DRUG/NDA:
NDA 18936 Prozac (fluoxetine) 10 mg, 20 mg, and 40 mg capsules (NDA 018936)
Sponsor: Eli Lilly and Company
Indication: Acute and maintenance treatment of major depressive disorder (MDD), acute and maintenance treatment of obsessive compulsive disorder (OCD), acute and maintenance treatment of bulimia nervosa, and acute treatment of panic disorder, with or without agoraphobia

Pending and recently approved Labeling
Supplements:

NDA	Supplement	Dated	Provides for	Status
18936	S-111	7/2/21	o Add reference to the change under RMC in Highlights o Add Sexual Dysfunction in Warnings and Precautions o Add "Sexual Dysfunction" to Patient Counseling Information (section 17). o Add "Sexual problems (dysfunction)" to the Medication Guide o Replace language in the Overdosage Section (10)	Pending
18936	S-109	6/26/18	PLLR Revisions	Approved 4/28/20

BACKGROUND

- On May 10, 2018, the Agency received a Citizen's Petition (CP, docket # FDA-2018-P-1846) from Data Based Medicine Americas, Ltd., requesting that FDA immediately revise all SSRI and SNRI labeling.
- After a careful collaborative review between DP, DUOG and OSE it was decided that the labels for SSRI (selective serotonin reuptake inhibitors) /SNRI (serotonin norepinephrine reuptake inhibitors) would be revised, and Safety Labeling Change (SLC) Notifications were issued on June 7, 2021. The letters required Applicants to incorporate labeling language pertaining to the association between use of these drugs with the occurrence of sexual dysfunction.
- In addition, the Agency requested revisions to the Overdosage Section (10) per

multiple discussions with the DARS team.

- The Application's July 2, 2021 submission did not comply with the requests in the 6/7/21 SLC letter. Labeling agreement was not reached during the dedicated "Discussion Period," so the Agency ultimately issued an Order letter.
- After the Agency issued an Order letter on 9/20/21, the sponsor agreed to the requested revisions and submitted labeling (on 09/27/21) consistent with the 6/7/21 SLC request.
- The Agency agreed to the following additional revisions to the labeling as requested by the Applicant:
  - In Section 11, removing "It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem®, fluoxetine hydrochloride)."
  - In Medication Guide the sexual dysfunction language (b) (4) (b) (4)

REVIEW

CBE: Yes
Reviews:

- Safety and Clinical Memo (E. Zerislassie, M. Stone, T. Farchione) dated 5/28/21 (entered in DARRTS under NDA 018936 Prozac)
- Office of Prescription Drug Promotion (D. Shah) review dated 5/11/21 (entered in DARRTS under NDA 018936 Prozac)
- Division of Medical Policy Programs/Patient Labeling (S. Hutchins) review dated 5/11/21(entered in DARRTS under NDA 018936 Prozac)

This supplement provides for revisions to the prescribing information and Medication Guide to align with the SLC letter we issued on 6/7/21.

- These supplements propose the following changes to the PI and MG for Prozac
  - Add reference to the change under RMC and W&P in Highlights and TOC
  - Add Sexual Dysfunction in Warnings and Precautions
  - Add "Sexual Dysfunction" to Patient Counseling Information (section 17).
  - Add "Sexual problems (dysfunction)" to the Medication Guide
  - Replace language under Section 10 Overdosage

CONCLUSIONS

1. These CBE labeling supplements only provide for the revisions as stated above when compared to the last approved labeling 4/8/20
2. The sponsor has incorporated our revisions, verbatim, as stated in the Agency's SLC letter dated 6/7/21.
3. I recommend that an approval letter issue for these pending supplemental applications.

{See appended electronic signature page}

CDR Ermias Zerislassie, Pharm.D., M.S.
Safety Regulatory Project Manager

{See appended electronic signature page}

Kimberly Updegraff, RPh, MS
Associate Director of Labeling

Attachment: annotated labeling, 10/5/21 concurrence email

35 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

From: Richard D Hoffman
To: Zerislassie, Ermias
Cc: Vishnu Vikash Sreedhar; Richard D Hoffman
Subject: RE: [EXTERNAL] RE: Response to Prozac SLC Order Letter NDA 18936
Date: Tuesday, October 5, 2021 4:44:55 PM

Hi Ermias,

Lilly has reviewed FDA's 05 October 2021 email response and (b) (4) [redacted] Lilly will implement FDA's request to place it under the section entitled 'What is the most important information I should know about PROZAC?'.

Please let me know if we should make a formal submission to the BLA reflecting this change to the Med Guide.

Thanks, Rich

Richard D. Hoffman, MS, RAC
Regulatory Advisor
Global Regulatory Affairs - US
Eli Lilly and Company
W: (317)-276-1241
C: (b) (6) [redacted]
F: (317)-276-1652
E: hoffman_richard_d@lilly.com

From: Zerislassie, Ermias <Ermias.Zerislassie@fda.hhs.gov>
Sent: Monday, October 4, 2021 4:23 PM
To: Richard D Hoffman <hoffman_richard_d@lilly.com>
Cc: Vishnu Vikash Sreedhar <sreedhar_vishnu_vikash@lilly.com>
Subject: [EXTERNAL] RE: Response to Prozac SLC Order Letter NDA 18936

Good Afternoon Richard,

As we were completing a labeling review of your submission we noted (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] Please provide concurrence to the attached MG (b) (4) [redacted]

[redacted] (b) (4).

From: Richard D Hoffman <hoffman_richard_d@lilly.com>
Sent: Wednesday, September 22, 2021 5:49 PM
To: Zerislassie, Ermias <Ermias.Zerislassie@fda.hhs.gov>
Cc: Vishnu Vikash Sreedhar <sreedhar_vishnu_vikash@lilly.com>; Richard D Hoffman <hoffman_richard_d@lilly.com>; Kiedrow, Keith <Keith.Kiedrow@fda.hhs.gov>; Patel, Hiren <Hiren.Patel@fda.hhs.gov>
Subject: [EXTERNAL] Response to Prozac SLC Order Letter NDA 18936
Importance: High

Hi Ermias,

The following is in response to FDA's recent Labeling Order letter (20 September 2021) and includes a Summary of Events as well a few questions regarding the proposed labeling. This communication will be formally submitted to the NDA as a General Correspondence on 23 September 2021. After consideration of the Summary of Events detailed below, Lilly respectfully requests a withdrawal of the Labeling Order as there was an inadvertent error during our 30 July 2021 (NDA 018936, SN 0140) submission to FDA. Additionally, we are seeking FDA alignment on a few minor changes to the proposed labeling FDA provided as part of the Labeling Order letter to make editorial corrections [redacted] (b) (4)

I appreciate the assistance and understanding regarding this situation. A response by 24 September 2021 would be appreciated to ensure we can provide an updated USPI for Prozac as soon as possible.

Thanks, Rich

-

-

Summary of Events

On 07 June 2021, FDA sent a Safety Label Change Notification letter (SCNL) to require safety-related label changes to the labeling of Prozac (fluoxetine) to address the risk of sexual dysfunction.

On 02 July 2021, Lilly submitted a prior approval supplement in response which proposed changes to the approved labeling to reflect the new safety information, but we did not agree with inclusion of sexual dysfunction as a new WARNINGS AND PRECAUTIONS.

On 26 July 2021 FDA disagreed with Lilly's proposal and concluded that "*SSRI/SNRI-related SD meets criteria for inclusion in the WARNINGS AND PRECAUTIONS section of labeling*", and further asked Lilly to "*submit the labeling in accordance with our 07 June 2021 letter by 30 July 2021*".

On 30 July 2021, Lilly submitted a response to FDA where we agreed to include SD in the

WARNINGS AND PRECAUTIONS section of labeling and also agreed to nearly all other proposals made by FDA (SN 0140). However, the draft USPI Lilly submitted as part of the 30 July 2021 amendment erroneously included the same draft USPI that was submitted to FDA on 02 July 2021. This was unintentional and we sincerely apologize for this error. See the attached Cover Letter and intended draft label associated with the 30 July 2021 submission.

On 27 September 2021, FDA issued a Labeling Order letter without reference to Lilly's 30 July 2021 submission.

Labeling Order – Proposals for Minor Edits to Labeling

With respect to the Labeling Order, we acknowledge FDA's request for a CBE submission and we have reviewed FDA's proposed USPI and Medication Guide modifications. Overall, we agree with the content and would like to expediate the review and approval process for these changes. We would appreciate FDA's comment on the following proposed changes such that we can submit the labeling without the need for further discussion. Specifically, Lilly would propose the following minor changes:

- Modification within the Highlights to reflect correct warning number (i.e., instead of 5.16, change to 5.17)
- Remove the Dosage & Administration (2.7) left border line as changes to this section are more than 1-year old (i.e., not a recent major change).
- Within Section 10, FDA proposed the following language:

> **10 OVERDOSAGE**
> The following have been reported with fluoxetine overdosage:
> • Seizures, which may be delayed, and altered mental status including coma.
> • Cardiovascular toxicity, which may be delayed, including QRS and QTc interval prolongation, wide complex tachyarrhythmias, torsade de pointes, and cardiac arrest. Hypertension most commonly seen, but rarely can see hypotension alone or with co-ingestants including alcohol.
> • Serotonin syndrome (patients with a multiple drug overdosage with other pro serotonergic drugs may have a higher risk).
>
> Gastrointestinal decontamination with activated charcoal should be considered in patients who present early after a fluoxetine overdose.
> Consider contacting a Poison Center (1-800-221-2222) or a medical toxicologist for additional overdosage management recommendations.

We agree with the proposed language; however, we recommend (b) (4) (b) (4) . Therefore, the following is being proposed:

10 OVERDOSAGE

(b) (4)

(b) (4)

[redacted]

- In Section 11, we recommend removing "It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem®, fluoxetine hydrochloride)." The proposal has been previously agreed upon by the agenc (b) (4) [redacted] FDA had commented: "*We agree with your proposal to remove the text referring to Sarafem in section 11.*"
- (b) (4) [redacted] we would propose that this language (b) (4) [redacted]

Please let me know by 24 September 2021 if FDA agrees with these proposed modifications and we will submit the CBE to the NDA.

Thanks again, Rich

Richard D. Hoffman, MS, RAC
Regulatory Advisor
Global Regulatory Affairs - US
Eli Lilly and Company
W: (317)-276-1241
C: (b) (6) [redacted]
F: (317)-276-1652
E: hoffman_richard_d@lilly.com

From: Zerislassie, Ermias <Ermias.Zerislassie@fda.hhs.gov>
Sent: Monday, September 20, 2021 10:25 PM
To: Richard D Hoffman <hoffman_richard_d@lilly.com>
Cc: Vishnu Vikash Sreedhar <sreedhar_vishnu_vikash@lilly.com>
Subject: [EXTERNAL] Prozac SLC order letter NDA 18936 S111

EXTERNAL EMAIL: Use caution before replying, clicking links, and opening attachments.

Good Evening Richard,

Please see the attached courtesy copy of a letter which you will soon receive in the mail.

From: Zerislassie, Ermias
Sent: Monday, July 26, 2021 9:28 AM
To: Richard D Hoffman <hoffman_richard_d@lilly.com>; Hillig, Meredith <Meredith.Hillig@fda.hhs.gov>
Cc: Vishnu Vikash Sreedhar <sreedhar_vishnu_vikash@lilly.com>
Subject: RE: [EXTERNAL] Response from FDA Regarding SLCN?

Good Morning Richard,

Please see the attached courtesy copy of the rebuttal response which you will soon receive in the mail.

From: Richard D Hoffman <hoffman_richard_d@lilly.com>
Sent: Monday, July 26, 2021 9:00 AM
To: Hillig, Meredith <Meredith.Hillig@fda.hhs.gov>; Zerislassie, Ermias <Ermias.Zerislassie@fda.hhs.gov>
Cc: Vishnu Vikash Sreedhar <sreedhar_vishnu_vikash@lilly.com>; Richard D Hoffman <hoffman_richard_d@lilly.com>
Subject: [EXTERNAL] Response from FDA Regarding SLCN?

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Hi Meredith & Errnias,

Late last week, the Division acknowledged Lilly's rebuttal and safety review associated with Cymbalta (duloxetine), and the Agency disagreed with the response.

Do either of you know the timing associated with FDA's response to Lilly's rebuttal for Prozac/Symbyax, as well as the separate response for Sarafem?

Please let me know when you have a minute as we are trying to coordinate our responses.

Thanks, Rich

Richard D. Hoffman, MS, RAC
Regulatory Advisor
Global Regulatory Affairs - US
Eli Lilly and Company
W: (317)-276-1241
C: (b) (6)
F: (317)-276-1652
E: hoffman_richard_d@lilly.com

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERMIAS ZERISLASSIE
10/06/2021 12:42:14 PM

KIMBERLY S UPDEGRAFF
10/06/2021 12:57:40 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

018936Orig1s111

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

NDA 18936/S-111

LABELING ORDER

Eli Lilly and Company
Attention: Richard D. Hoffman, MS, RAC
Advisor, Global Regulatory Affairs – US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Mr. Hoffman:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Prozac (fluoxetine) capsules.

On June 7,2021, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety-related label changes to the labeling of Prozac (fluoxetine) to address the risk of sexual dysfunction. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On July 2, 2021, you submitted a prior approval supplement proposing changes to the approved labeling to reflect the new safety information.

Section 505(o) requires FDA to promptly review your submission and initiate discussions if necessary. You were contacted on July 26, 2021, to initiate discussions of your submission.

We have completed the review of your submission dated July 2, 2021, initiated discussions of your submission and did not reach agreement, and find that your proposed labeling changes do not adequately address the new safety information described above.

Under the authority of Section 505(o)(4)(E) of the FDCA, we are ordering you to make all of the changes in the labeling listed in the June 7, 2021, letter (attached).

Pursuant to Section 505(o)(4)(E), a changes being effected (CBE) supplement containing all of the changes to the labeling that are listed in the June 7, 2021, letter must be received by FDA by October 5, 2021, for Prozac.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

Alternatively, by September 25, 2021, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75 and the guidance for industry *Formal Dispute Resolution: Appeals Above the Division Level*.[1] The appeal should be submitted as a correspondence to your NDA referenced above. Identify the submission as "**Formal Dispute Resolution Request**" both on the cover letter and on the outside envelope. A copy of the submission should be sent to:

Melissa Sage
CDER Formal Dispute Resolution Project Manager
Food and Drug Administration
Office of New Drugs
Building 51, Room 6158
10903 New Hampshire Avenue
Silver Spring, MD 20993

In addition, to expedite coordination of any such appeal, a copy of the submission should also be sent to:

Ermias Zerislassie
Safety Regulatory Project Manager
Food and Drug Administration
Division of Psychiatry
Building 22, Room 4380
10903 New Hampshire Avenue
Silver Spring, MD 20993

Refer to the guidance for industry *Formal Dispute Resolution: Appeals Above the Division Level* for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Melissa Sage, CDER Formal Dispute Resolution Project Manager, at 301-796-6449. Appeals received by the Agency later than September 25 2021, will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4), in the amount of up to $250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your product to be misbranded under section 502(z) of the Act, 21

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S.C. 352(z), which could subject you to additional enforcement actions, including but not limited to seizure of your product and injunction.

If you have any questions, call Ermias Zerislassie, Safety Regulatory Project Manager, at 301-796-2770.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S): Safety Labeling Change Notification Letter

- Redlined Prescribing Information Text
- Redlined Medication Guide Text

35 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM H Dunn
09/20/2021 09:55:09 PM

NDA 018936
NDA 021520

SAFETY LABELING CHANGE NOTIFICATION

Eli Lilly and Company
Attention: Richard D. Hoffman, MS, RAC
Advisor, Global Regulatory Affairs – US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Mr. Hoffman:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Prozac (fluoxetine capsules) and Symbyax (olanzapine and fluoxetine) capsules.

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product.

Since Prozac was approved on December 29, 1987, we have become aware of post marketing reports in the FDA Adverse Event Reporting System (FAERS) and biomedical literature that suggest an association between the use of selective serotonin reuptake inhibitors (SSRI) and the occurrence of sexual dysfunction. We have determined that SSRI and SNRI products represent classes of products that have the potential for the same serious risk of sexual dysfunction. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above and, we believe that the new safety information should be included in the labeling for all SSRI and SNRI as follows:

Highlights

----------**WARNINGS AND PRECAUTIONS** ----------

- Sexual Dysfunction: DRUG X use may cause symptoms of sexual dysfunction (5.X)

5 WARNINGS AND PRECAUTIONS

5.X Sexual Dysfunction

Use of SSRIs, including DRUG X, may cause symptoms of sexual dysfunction *[see Adverse Reactions (6.X)]*. In male patients, SSRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SSRI use may result in decreased libido and delayed or absent orgasm.

It is important for prescribers to inquire about sexual function prior to initiation of Drug X and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Sexual Dysfunction

Advise patients that use of DRUG X may cause symptoms of sexual dysfunction in both male and female patients. Inform patients that they should discuss any changes in sexual function and potential management strategies with their healthcare provider *[see Warnings* and *Precautions (5.X)].*

MEDICATION GUIDE

- **Sexual problems (dysfunction).** Taking selective serotonin reuptake inhibitors (SSRIs), including DRUG X, may cause sexual problems.

  Symptoms in males may include:
  - o Delayed ejaculation or inability to have an ejaculation
  - o Decreased sex drive
  - o Problems getting or keeping an erection

  Symptoms in females may include:
  - o Decreased sex drive
  - o Delayed orgasm or inability to have an orgasm

  Talk to your healthcare provider if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with DRUG X. There may be treatments your healthcare provider can suggest.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified above, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that above, submit a prior approval supplement (PAS).

FDA intends to approve a labeling change common to all class members on the same day. In accordance with this policy, we have determined that an extension of the discussion period will be warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for your supplement or rebuttal statement will begin when the submission is received, and will end by September 5, 2021, unless additional discussion extensions are warranted.

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED)."

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

We remind you that requirements under section 505(o)(4) also apply to any authorized generic products marketed under this NDA.

OTHER LABELING CHANGES
Although not part of this safety labeling notification, we are also taking the opportunity to update the OVERDOSAGE section of the product labeling. We request that you also submit these changes when you submit your supplemental application.

10 OVERDOSAGE

The following have been reported with fluoxetine tablet overdosage:

- Seizures, which may be delayed, and altered mental status including coma.
- Cardiovascular toxicity, which may be delayed, including QRS and QTc interval prolongation, wide complex tachyarrhythmias, torsade de pointes, and cardiac arrest. Hypertension most commonly seen, but rarely can see hypotension alone or with co-ingestants including alcohol.
- Serotonin syndrome (patients with a multiple drug overdosage with other pro-serotonergic drugs may have a higher risk).

Gastrointestinal decontamination with activated charcoal should be considered in patients who present early after a fluoxetine overdose.

Consider contacting a Poison Center (1-800-221-2222) or a medical toxicologist for additional overdosage management recommendations.

If you have any questions, call Ermias Zerislassie, Safety Regulatory Project Manager, at (301) 796-2770.

Sincerely,

{See appended electronic signature page}

Marc Stone, M.D.
Deputy Director for Safety
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARC B STONE
06/07/2021 01:04:44 PM

The Division acknowledges Lilly's rebuttal and safety review titled "Regulatory Response: Information Request Selective Serotonin Reuptake Inhibitors (SSRI) and Selective Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs) dated on 19 Dec 2018. The Agency disagrees with Lilly's rebuttal response.

The Agency conducted a review of sexual dysfunction (SD) in all SSRIs/SNRIs. It concluded SSRI/SNRI-related SD meets criteria for inclusion in the WARNINGS AND PRECAUTIONS section of labeling, based on following factors:

1. In registered RCTs, decreased or loss of libido, erectile dysfunction and ejaculation in men, and delayed or absent orgasm in women are reported in higher rates than placebo for most of SSRIs/SNRIs. Enough evidence supports causal correlation between SSRIs/SNRIs and specific sexual dysfunction (SD) adverse effects (AEs) during treatment: disorders of libido (decreased libido or loss of libido), arousal disorder in men (erectile dysfunction), ejaculation disorder in men (ejaculation delay or failure) and orgasm disorder in women (delayed or absent orgasm).

2. SD AE frequency, severity, and associated complications (non-adherence, discontinuation, relapse, increased disease severity, and risk of serious outcomes), increased SD risk compared to other antidepressants, and the importance of sexual functioning and SD to patients.[i,ii] Evidence suggests that many clinicians do not have a full understanding of the risks, do not adequately communicate the risk of SD with patients before or during treatment, and do not adequately communicate with patients about potential contributory factors and potential treatment options and management of SD[iii,iv.] Including information about SD in the WARNINGS AND PRECAUTIONS sections of labeling, emphasizing the risks and management issues more prominently, could improve understanding, communication, monitoring, and management of the risks and enhance collaboration between patients and clinicians, which could improve the success of antidepressant treatment and potentially mitigate against serious risks of inadequate treatment of depression and other psychiatric disorders, such as relapse, worsening of disease severity, and suicidality. This could be beneficial for patients and clinicians.

Please submit the labeling in accordance with our 07 June 2021 letter by 30 July 2021. Thank you

---

[i] Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999; 281:537-544.

[ii] Clayton AH, El Haddad S, Iluonakhamhe J, Ponce Martinez C, Schuck AE. Sexual dysfunction associated with major depressive disorder and antidepressant treatment. *Expert Opinion Drug Safety* 2014;13(10):1361-1374.

[iii] Montejo AL, Calama J, Rico-Villademoros F, Montejo L et al. A Real-World Study on Antidepressant-Associated Sexual Dysfunction in 2144 Outpatients: The SALSEX I Study. *Archives of Sexual* Behavior, 2019,48:923-933.

[iv] Bahrick AS Harris MM. Sexual Side Effects of Antidepressant Medications: An Informed Consent Accountability Gap. *J Contemp Psychother*, 2009;39:135-143.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERMIAS ZERISLASSIE
07/26/2021 10:24:59 AM