

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>.

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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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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:

- 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 DRUG X. There may be treatments your healthcare provider can suggest.

U.S. Food and Drug Administration

Silver Spring, MD 20993

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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:

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

**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 overdose:

- 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 overdose 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 overdose 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