"Grewal, Renmeet" <Renmeet.Grewal@fda.hhs.gov>

02-May-2007 10:42

To barbara.e.arning@gsk.com
cc
Subject FW: Adult suicidality letter

Hi Barbara,
I just wanted to make sure you received a copy of this.

-Rimmy

Renmeet Grewal, Pharm.D., LCDR USPHS
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Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
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From: Grewal, Renmeet
Sent: Wednesday, May 02, 2007 9:40 AM
To: 'mary.e.martinson@gsk.com'
Subject: Adult suicidality letter

Dear Mary,
Please refer to the Advisory Committee meeting held on December 13, 2006 regarding adult suicidality data in antidepressants drugs. The Agency has come to a decision with final language for the prescriber labeling and Medication Guide (MG). Attached is a supplement request letter with the new language. We are requesting that sponsors submit revised prescriber labeling and MG, verbatim, as outlined in the attached letter within 30 days from today.

As for the Paxil letter, the Agency issued an approvable letter responding to your CBE letters.

Additionally, the Agency will be announcing these changes in the form of a Press Release later on today.

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

Sincerely,
Rimmy

<<wellbutrin asl.pdf>> <<parnate asl.pdf>> <<paxil ae letter.pdf>>

Renmeet Grewal, Pharm.D., LCDR USPHS
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Division of Psychiatry Products
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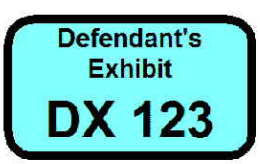

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-031/S-053
NDA 20-710/S-017
NDA 20-936/S-029

GlaxoSmithKline
Attention: Barbara E. Arning, M.D.
Senior Director, US Regulatory Affairs, Psychiatry
2301 Rennaissance Boulevard, P.O. Box 61540
King of Prussia, PA 19406-2772

Dear Dr. Arning:

We acknowledge receipt of your supplemental new drug applications dated April 27, 2006, and received April 28, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil (paroxetine hydrochloride) tablets (NDA 20-031), Paxil CR (paroxetine hydrochloride) controlled-release tablets (NDA 20-936), and Paxil (paroxetine hydrochloride) suspension (NDA 20-710).

These supplements, submitted under "Changes Being Effected", provide for labeling revisions to the WARNINGS and Information for Patients sections regarding suicidality in young adults based upon your analysis of the paroxetine adult suicidality data.

We have completed our review of your supplemental applications, and they are approvable. Before these applications may be approved, you will need to make revisions to your labeling, as outlined below, so as to ensure standardized labeling pertaining to adult suicidality with all of the drugs to treat major depressive disorder (MDD)

We additionally refer to the December 13, 2006 meeting of the Psychopharmacologic Drugs Advisory Committee to discuss FDA's meta-analysis of suicidality data derived from placebo-controlled trials of antidepressants in adult patients with major depressive disorder and other psychiatric disorders.

Based upon the recommendations made by the committee, we believe that additional changes are needed in antidepressant labeling and medication guides to alert practitioners, patients, family members and caregivers about an increased risk of suicidal thinking and behavior (suicidality) in young adults with MDD and other psychiatric disorders who are taking antidepressant medications. Changes are also needed to inform practitioners about an apparent favorable effect of antidepressants on suicidality in older adults and to remind them that the disorders being treated with antidepressants are themselves associated with an increased risk of suicidality.

Therefore, we are requesting revisions to your labeling and the antidepressant medication guides to incorporate the committee's recommendations. Specifically, we are requesting the changes below in product labeling and the Medication Guide.

Revisions to Product Labeling

[These changes should be made to the box warning at the beginning of the package insert.]

DRUG NAME

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert established name] is not approved for use in pediatric patients. (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

[The following changes should be made to the current language under the **WARNINGS-Clinical Worsening and Suicide Risk** section.]

WARNINGS-Clinical Worsening and Suicide Risk

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

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults

with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs 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 [add table number].

Table [add table number]	
Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Drug-Related Increases
<18	14 additional cases
18-24	5 additional cases
	Drug-Related Decreases
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

PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with [Insert drug name], for a description of the risks of discontinuation of [Insert established name]).

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 [Insert established name] should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: 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 above 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 [Insert established name] is not approved for use in treating bipolar depression.

> [The following changes should be made in current language under the **PRECAUTIONS-Information for Patients** section.]

PRECAUTIONS-Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with [Insert established name] and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for [Insert established name]. The prescriber or health professional 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. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking [Insert established name].

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Revisions to Medication Guide

Medication Guide
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults when the medicine is first started.**

2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is first started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

   Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

   - thoughts about suicide or dying
   - attempts to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling very agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses
   - an extreme increase in activity and talking (mania)

- other unusual changes in behavior or mood

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What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

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

Simultaneous with this action letter, FDA has issued a Press Release as well as updated our internet site with the revised Medication Guides to alert the community to this action. Since there are so many MDD products, we feel that these actions are a better way to alert the community than individual Dear Health Care Professional (DHCP) letters for each of these products. Thus, we are not requesting individual DHCP letters.

These labeling revisions should be submitted as a formal amendment to your supplemental applications within 30 days from the date of this letter.

If you have any questions, call Renmeet Grewal, Pharm. D., Regulatory Project Manager, at (301) 796-1080 or Bill Bender, Regulatory Project Manager, at 301-796-2145.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
5/1/2007 04:49:57 PM