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21-Jun-2007 09:11

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Subject Wellbutrin, Paxil, Parnate Adult suicidality class labeling changes

Good Morning,

Please refer to our letter dated 5-1-07, requesting class labeling revisions for all drugs to treat major depressive disorder.

We have completed our review of all of these responses, and we believe, based upon these responses, that the labeling needs to be further edited as follows (strike through font denotes deletions to our labeling and double underline font denotes additions):

1. In Table X under **WARNINGS-Clinical Worsening and Suicide Risk**, we believe that the table descriptor under "Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated" should be revised as follows:

· "Drug Related Increases" to "Increases Compared to Placebo"
"Drug Related Decreases" to "Decreases Compared to Placebo"

2. In the Medication Guide, we have deleted the phraseology related to "first", as denoted below, since "first" could represent a misleading concept for the patient.

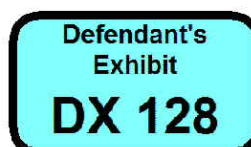
· Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults ~~when the medicine is first started~~ within the first few months of treatment.

· 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.

Additionally, some of the sponsors have inadvertently omitted the class labeling paragraph starting with "Consideration should be given..." under the **WARNINGS-Clinical Worsening and Suicide Risk** section, and some sponsors have incorrectly added the discontinuation language paragraph starting with "If the decision has been made..." to this section. Attached to this e-mail is the correct labeling, incorporating the above changes, for your product.

We have also noted that some sponsors have taken this opportunity to include other revisions to their labeling which are not applicable to the class labeling revisions requested in our 5-1-07 letter. We are requesting that these changes be submitted as a separate supplement.

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In an attempt to take a final action on your supplemental applications, the Agency would like to secure labeling agreement with you via e-mail. Please be reminded that it is critical that the labeling is consistent for all of these products. As noted above, the relevant sections of the prescriber labeling as well as the entire Medication Guide are attached to this e-mail.

We request that you respond to this e-mail within a week.

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

Regards,
Rimmy

<<Revisions to Parnate Labeling 6-19-07.doc>> <<Revisions to Paxil Labeling 6-19-07.doc>>
<<Revisions to Medication Guide 6-19-07.doc>> <<Revisions to Wellbutrin, SR, XL Labeling 6-19-07.doc>> <<Revisions to Wellbutrin Medication Guide 6-19-07.doc>>

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DX 128-002

Revisions to Product Labeling

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

Paxil

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 Paxil 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. Paxil 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.

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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 <u>Compared to Placebo</u>
<18	14 additional cases
18-24	5 additional cases
	Drug-Related-Decreases <u>Compared to Placebo</u>
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

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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 Paxil, for a description of the risks of discontinuation of Paxil.

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 Paxil 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 Paxil 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 Paxil 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 Paxil. The prescriber or health professional should instruct

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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 Paxil.

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.

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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~~ within the first few months of treatment.**
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.

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