May 2004

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IMPORTANT DRUG INFORMATION

Dear Healthcare Professional:

On March 22, 2004, the FDA issued a Public Health Advisory cautioning physicians, their patients, and families about the need to closely monitor all patients being treated with antidepressants.[1] This Advisory arose from the FDA's ongoing review of potential safety issues involving antidepressants and pediatric patients; additional information concerning this review is expected later this year. The FDA also announced that it was proposing labeling changes for ten antidepressants: Prozac® (fluoxetine), Zoloft® (sertraline), Paxil® (paroxetine), Luvox® (fluvoxamine), Celexa® (citalopram), Lexapro® (escitalopram), Wellbutrin® (bupropion), Effexor® (venlafaxine), Serzone® (nefazodone), and Remeron® (mirtazepine). These labeling changes, which have now been finalized, describe that patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications. The changes include a new warning recommending close observation of adult and pediatric patients treated with antidepressant drugs for worsening depression or the emergence of suicidality, particularly at the beginning of treatment or at the time of dose increases or decreases.

GlaxoSmithKline, in consultation with the FDA, would like to advise you of the new warnings in the labeling for WELLBUTRIN® (bupropion hydrochloride) Tablets, WELLBUTRIN SR® (bupropion hydrochloride) Sustained-Release Tablets, and WELLBUTRIN XL™ (bupropion hydrochloride extended-release tablets), indicated for the treatment of major depressive disorder in adults. These products are not approved for use in the pediatric population. Revisions have been made to the WARNINGS and PRECAUTIONS sections of labeling to reflect the new warning for all the aforementioned bupropion products, as well as to the Patient Information Leaflet that appears at the end of the labeling for these products. **Please read the full text of the added WARNINGS and PRECAUTIONS following this letter.** A full copy of the revised package insert for WELLBUTRIN XL is enclosed.

Be aware of other products containing the same active ingredient as WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL. ZYBAN® (bupropion hydrochloride) Sustained-Release Tablets is indicated as an aid to smoking cessation treatment in adults. This product is not approved for use in the pediatric population. Although ZYBAN is not indicated for the treatment of depression, this new warning information has also been added to the product label and Patient Information Leaflet for ZYBAN.

The medical community can further our understanding of WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL and ZYBAN by reporting adverse events to GlaxoSmithKline at 1-888-825-5249 or to the FDA MEDWATCH program by phone at 1-800-FDA-1088, by FAX at 1-800-FDA-0178, by modem at 1-800-FDA-7737 or by mail:

MEDWATCH HF-2
FDA
5600 Fisher's Lane
Rockville, MD 20857

[1] For further information on the FDA Public Health Advisory please refer to the FDA's website at: http://www.fda.gov/cder/drug/antidepressants/AntidepressanstPHA.htm

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GlaxoSmithKline encourages you to familiarize yourself with these revisions to labeling. If you have any questions about the new information, please contact our Medical Information Department at 1-888-825-5249.

Sincerely,

Alan Metz, M.D.
V.P., Medical
Worldwide Development, North America

WARNINGS-Clinical Worsening and Suicide Risk

Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

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, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

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, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Prescriptions for WELLBUTRIN 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 WELLBUTRIN is not approved for use in treating any indications in the pediatric population.

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 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 WELLBUTRIN is not approved for use in treating bipolar depression.

PRECAUTIONS-Information for Patients

Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's physician, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.