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at screening for hepatitis B (surface antigen–positive) and/or C (hepatitis C antibody–positive).

• Among the co-infected patients, elevations in aspartate transaminase (AST) to greater than five times the upper limit of normal developed in 13% of the efavirenz patients and in 7% of the controls.

• Elevations in alanine transaminase (ALT) to greater than five times the upper limit of normal occurred in 20% of the efavirenz patients and in 7% of the controls.

• Among co-infected patients, 3% of the patients receiving efavirenz-containing regimens and 2% of controls withdrew from the study because of liver or biliary system disorders.

Lipids

• Increases from baseline in total cholesterol of 10% to 20% were observed in some uninfected volunteers receiving efavirenz.

• In patients treated with efavirenz + zidovudine + lamivudine, nonfasting total cholesterol and high-density lipoprotein (HDL) cholesterol levels increased by approximately 20% and 25%, respectively, from baseline values.

• In patients receiving efavirenz + indinavir, nonfasting cholesterol and HDL cholesterol levels increased by approximately 40% and 35%, respectively.

• Nonfasting total cholesterol levels above 240 mg/dl and above 300 mg/dl were reported as follows:
  - In 34% and 9%, respectively, of patients treated with efavirenz + zidovudine + lamivudine
  - In 54% and 20%, respectively, of patients treated with efavirenz + indinavir
  - In 28% and 4%, respectively, of patients treated with indinavir + zidovudine + lamivudine

• The effects of efavirenz on triglycerides and low-density lipoprotein (LDL) cholesterol were not well characterized because samples were taken from nonfasting patients. The clinical significance of these findings is unknown.

Conclusion: Efavirenz is an important therapeutic agent for treating acquired immunodeficiency syndrome (AIDS). Even though the agent cannot cure or prevent HIV infection or AIDS, it inhibits the virus from reproducing and appears to slow down the destruction of the immune system.

Efavirenz does not prevent the spread of infection to other people. Patients receiving efavirenz may continue to have some of the problems usually related to AIDS or HIV infection. In deciding whether to use a medication, patients and their physicians must weigh the risks against the benefits.

Rituximab (Rituxan®)

Manufacturer: Biogen and Genentech

Indications: Rituximab is indicated for relapsed or refractory low-grade or follicular, CD20-positive, B-cell non-Hodgkin’s lymphoma and for diffuse, CD20-positive, large B-cell non-Hodgkin’s lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy.

Reason for FDA Intervention: Very rare cases (less than one adverse drug event per 10,000 treated patients) of hepatitis B virus (HBV) reactivation in association with rituximab therapy were reported internationally. Most patients received rituximab in combination with chemotherapy. Isolated cases have been reported in patients who either had evidence of antibodies against hepatitis B surface antigen before treatment or did not have any such antibodies. Reporting rates determined on the basis of spontaneously reported postmarketing adverse events are generally presumed to underestimate the risks associated with drug treatments. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.

Label Change: HBV reactivation with fulminant hepatitis, hepatic failure, and death have been reported in some patients with hematological malignancies who received rituximab. Most patients received this drug in combination with chemotherapy.

Persons at high risk for HBV infection should be screened before they begin rituximab therapy. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following therapy.

If viral hepatitis develops, rituximab and any concomitant chemotherapy should be discontinued; appropriate treatment, including antiviral therapy, should be initiated. Whether it is safe to resume rituximab therapy in patients who develop hepatitis subsequent to HBV reactivation is unclear.

Conclusion: Reactivation of HBV infection is a well-known complication in patients with chronic hepatitis B, especially in those receiving cytotoxic or immunosuppressive therapy. Non-Hodgkin’s lymphoma itself may be an independent risk factor for HBV reactivation. Carriers of hepatitis B, and patients with evidence of having recovered from hepatitis B infection, should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and up to one year following rituximab therapy.

Levothyroxine (Levoxyl®)

Manufacturer: Jones Pharma, Inc.

Indications: Levothyroxine has several uses:

• As replacement or supplemental therapy in patients with congenital or acquired hypothyroidism of any cause, except transient hypothyroidism during the recovery phase of subacute thyroiditis.

• Suppression of pituitary thyroid-stimulating hormone (TSH) to treat or prevent various types of euthyroid goiters, subacute or chronic lymphocytic thyroiditis (e.g., Hashimoto’s thyroiditis), or multinodule goiter.

• As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent, well-differentiated thyroid cancer.

Rationale for Labeling Change: Levothyroxine tablets may cause choking or gagging or may become stuck in the throat if they are not taken with sufficient amounts of water. Without water, the tablets may rapidly swell and begin to dissolve. Most of the problems related to swallowing disappeared when a full glass of water was consumed.

Precautions Section: A warning has been issued to remind patients to swallow the tablets with a full glass of water.

Adverse Reactions Section: Choking, gagging, difficulty
swallowing, and tablets sticking in the throat occurred when the tablets were not taken with water.

**Dosage and Administration Section:** Levoxyl should be taken with water.

**Conclusion:** Patients assume that because the tablets are small, they would be easy to swallow without water. Unfortunately, this is not the case. For quality and safety purposes, the pharmacist should inform patients about the need to drink water when taking this medication.

**Zoledronic Acid (Zometa®)**

**Manufacturer:** Novartis

**Indications:** Zoledronic acid injection is indicated for patients with hypercalcemia of malignancy, for patients with multiple myeloma, and for patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should improve after treatment with at least one hormonal therapy.

**Reason for Labeling Change:** Cases of osteonecrosis (primarily involving the jaws) have been reported in patients treated with bisphosphonates, including zoledronic acid. Most reported cases have been in patients who were undergoing dental procedures, such as tooth extraction, and who were also receiving cancer treatment, including chemotherapy and corticosteroids. Osteonecrosis of the jaw is associated with multiple well-documented risk factors, including a cancer diagnosis; concomitant therapies (e.g., chemotherapy, radiotherapy, and corticosteroids); and additional conditions (e.g., anemia, blood clot disorders, infection, and pre-existing dental disease).

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with risk factors for osteonecrosis. While receiving treatment for cancer, these patients should avoid invasive dental procedures if possible. If jaw osteonecrosis occurs during bisphosphonate therapy, dental surgery may exacerbate the condition. For patients who require dental procedures, it is not clear whether discontinuation of bisphosphonate treatment might reduce the risk of jaw osteonecrosis.

**Action Taken:** Revisions under the Precautions and Adverse Reactions sections of labeling describe spontaneous reports of osteonecrosis of the jaw mainly in cancer patients who have received bisphosphonates as a component of their therapy. Appropriate preventive dentistry should be considered before patients are given bisphosphonates if they have concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids, or poor oral hygiene).

**Conclusion:** These revisions are essential for the potential safety issues that can arise with the use of zoledronic acid in patients with multiple myeloma. Preventive dental treatment should be considered before bisphosphonates are given to patients with concomitant risk factors for osteonecrosis. Patients who have been taking zoledronic acid for months may require a different approach.

In general, patients should inform their dentist if they are taking bisphosphonates. These patients should be monitored carefully, and some dentists have recommended it. Some patients might even consider discontinuing bisphosphonate therapy before they undergo a dental procedure.

**Infliximab (Remicade®)**

**Manufacturer:** Centocor

**Indication:** This agent is used to treat patients with rheumatoid arthritis and Crohn's disease.

**Reason for FDA Intervention:** In controlled studies of all tumor necrosis factor-α (TNF-α)–blocking agents, including infliximab, more cases of lymphoma have been observed in patients taking the agents than in control patients. Malignancies have also been observed in open-label, uncontrolled clinical studies at a rate several-fold higher than that expected in the general population. Patients with Crohn’s disease or rheumatoid arthritis, particularly those with highly active disease or chronic exposure to immunosuppressant therapies, may be at a higher risk than others for the development of lymphoma.

**Label Change:** The FDA recommends that a warning concerning malignancy be added to the labeling for all therapeutic agents that block TNF.

**Antidepressants**

**Label Change**

**Black Box Warning**

**Suicidality in Children and Adolescents.** Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be 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. [Drug Name] is not approved for use in pediatric patients except for patients with [any approved pediatric claims here]. (See Warnings and Precautions: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events [with the] drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

**Warnings: Clinical Worsening and Suicide Risk**

The following language would replace the current language.

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. There has been a longstanding 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 suicidality has been established in pediatric patients.

Pooled analyses of short-term placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a
total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events [with the] drug was 4%, twice the placebo risk of 2%.

There was considerable variation in risk among drugs but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from trials in other psychiatric indications (obscene compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use (i.e., beyond several months). It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be 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. Ideally, such observation would include at least weekly face-to-face contact with patients or their family members or caregivers during the first four weeks of treatment, then biweekly visits for the next four weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, 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.

Families and caregivers of pediatric 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 [Drug Name] should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

This language will be included for those drugs for which tapering is recommended.

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 [Drug Name]), for a description of the risks of discontinuation of [Drug Name].

Rule out bipolar disorder to the extent possible. 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.

Precautions: Information for Patients

The following language would replace the current language.

Physicians should inform patients and caregivers about the benefits and risks associated with treatment with [Drug Name] and should counsel them in its appropriate use. A patient Medication Guide is available for [Drug Name]. The prescriber should instruct patients 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.

... Physicians are advised to discuss the following issues with patients for whom they prescribe [Drug Name] and to ask them to alert their physician if these occur:

Clinical Worsening and Suicide Risk. 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, 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 observe [patients] 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 physician, 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.

Pediatric Use. This section will include either (1) a general statement for drugs for which pediatric data have not been submitted to [the] FDA, as follows: “Safety and effectiveness in the pediatric population have not been established (see Box Warning and Warnings: Clinical Worsening and Suicide Risk),” or (2) more specific language regarding pediatric efficacy data that have been evaluated by [the] FDA.