



## FDA Requests Antidepressant Labeling Add Suicidality Warning

FDA is requesting that labeling for 10 antidepressants include a warning recommending close monitoring of adult and pediatric patients for suicidal behavior.

"Health care providers should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose either increases or decreases," a March 22 FDA Public Health Advisory says.

The advisory and requested labeling changes are in response to recommendations made by the Psychopharmacological Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee Feb. 2 ("The Pink Sheet" Feb. 9, 2004, p. 35).

The committee urged FDA to issue stronger warnings about the medications' possible risks as it awaits the results of a data reanalysis on a possible link between antidepressants and pediatric suicidality.

The warning proposed by the agency notes that "although FDA has not concluded that these drugs cause worsening depression or suicidality, health care providers should be aware that worsening of symptoms could be due to the underlying disease or might be a result of drug therapy."

FDA is requesting the labeling change for 10 drugs: Lilly's **Prozac** (fluoxetine), Forest's **Celexa** (citalopram) and **Lexapro** (escitalopram), Wyeth's **Effexor** (venlafaxine), GlaxoSmithKline's **Paxil** (paroxetine) and **Wellbutrin** (bupropion), Pfizer's **Zoloft** (sertraline), Bristol-Myers Squibb's **Serzone** (nefazodone), Solvay's **Luvox** (fluvoxamine), and Organon's **Remeron** (mirtazapine).

The proposed warning highlights anxiety, agitation, akathisia and other symptoms to monitor, noting that "there is concern that patients who experience one or more of these symptoms may be at increased risk for worsening depression or suicidality." The advisory committee recommended that analysis of pediatric antidepressant data include examination of these "activation" symptoms ("The Pink Sheet" Feb. 16, 2004, p. 38).

FDA's suggested labeling change also urges screening of patients for bipolar disorder before initiating

treatment with antidepressants, because the drugs may induce manic episodes in bipolar patients.

The agency noted that it is prepared to meet with companies individually about the labeling change but expects its warning language to be adopted without substantive modifications.

"We'll listen to the individual companies to see if they have any changes they think should be made...but at the moment, I can see no reason why we would adopt different language for different drugs," FDA Neuropharmacologic Drug Products Division Director Russell Katz, MD, said on a March 22 conference call.

**Labeling changes are expected to be consistent across all antidepressants.**

"The concerns cross all the drugs that we've sent a letter to.... We would hope that, at the end, we would have language that all sponsors would adopt."

Although the labeling changes are not required and may take time to implement,

FDA noted that publicity surrounding the public health advisory was crucial. "At the moment, we are...counting on the fact that these proposed changes are being announced publicly, so that family members, as well as the physicians...are aware that we have made this request and that we have these concerns," Katz said.

In June 2003, FDA issued a "Talk Paper" cautioning against off-label use of Paxil to treat major depressive disorder in children due to the possibility of increased suicidal behavior ("The Pink Sheet" June 16, 2003, p. 23). FDA expanded the warning in October 2003 ("The Pink Sheet" Nov. 3, 2003, p. 11).

Wyeth revised Effexor labeling in August to include a precaution on reports of hostility and suicide-related adverse events in pediatric clinical trials ("The Pink Sheet" Sept. 8, 2003, p. 6).

Because possible suicide-related events are poorly described in existing study data, a data reanalysis is underway by a Columbia University group; results are expected this summer ("The Pink Sheet" Jan. 26, 2004, p. 7). FDA is also planning a guidance on approaches for ascertaining suicidality in future trials.

Congressional committees are investigating allegations that the agency suppressed information linking the drugs with suicidal behavior (*see following story*). ♦ ♦