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F.D.A. Toughens Warning on Antidepressant Drugs

By GARDINER HARRIS

Heeding the recommendation of an advisory committee, the Food and Drug Administration ordered pharmaceutical companies yesterday to add strong warnings to antidepressants, saying the drugs could cause suicidal thoughts and actions in some children and teenagers.

The so-called black-box warnings will appear in boldface type, framed by a black border, on information sheets for patients and doctors. They are the toughest requirement that federal drug regulators can impose short of banning a medication.

Black-box warnings accompany hundreds of other drugs. But in this case the agency also directed the manufacturers to print and distribute medication guides with every antidepressant prescription, to inform patients of the risks. Such guides are required for fewer than 30 other drugs.

The agency's decision came after a year of intense controversy about antidepressants and one month after the advisory committee concluded that evidence linking them with suicidal behavior in children and adolescents was sufficient to warrant the strengthened warnings.

Though the overall risk of suicide is low, children and teenagers who take antidepressants appear twice as likely as those given placebos to become suicidal, according to studies. If 100 patients are given the drugs, 2 or 3 more will become suicidal than would have had they been given placebos, the studies suggest.

Many critics of the drugs said they were pleased by the agency's action.

"This is a milestone that a lot of us were concerned would never happen," said Karen Barth Menzies, a plaintiffs' lawyer who testified at hearings that the advisory committee held on the drugs.

But she and others said the agency had been too slow to act, and some said the warnings did not go far enough. Tom Woodward, whose 17-year-old daughter committed suicide last summer, a week after starting therapy with the antidepressant Zoloft, said she might still be alive had the F.D.A. acted earlier.

"How many other lives have been lost while they dragged their feet?" Mr. Woodward asked.

For its part, the American Psychiatric Association, the specialty's medical society, issued a statement repeating its "deep concern that a black-box warning on antidepressants may have a chilling effect on appropriate prescribing for patients."

"This," the statement continued, "would put seriously ill patients at grave risk."

Psychiatrists across the country have been deeply divided about how to respond to the revised view of antidepressants. Many maintain that untreated depression poses a far graver risk of suicide in children and teenagers than the risk posed

by the drugs. The number of teenagers and children being prescribed antidepressants in the United States has dropped 18 percent this year amid concerns over the antidepressants, according to a large provider of drug benefits.

Still, many psychiatrists were pleased that federal drug regulators were ending the uncertainty surrounding the medicines. The black-box warning "is probably a little overcautious, but you have to start somewhere," said Dr. Laurence Greenhill, a professor of clinical psychiatry at Columbia University.

The warnings will be added to all antidepressants, not just to the newer generation of drugs that has been a focus of much of the controversy. The agency has yet to make final the language of the patient medication guides, but the wording of the black-box warning is stark.

"Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents," the warning begins. It goes on to recommend that patients given the pills be closely observed, and notes that few antidepressants have proved effective against depression in children and teenagers.

The agency's action will most likely have a chilling effect on antidepressant advertising. So-called reminder ads - advertising that includes only a drug's name and not its use - will be banned for antidepressants. In other ads, the entire black-box warning must be either prominently printed on the ad or, for radio and television, spoken clearly during the commercial.

Dr. Joseph Feczko, president for development at Pfizer Inc., which makes Zoloft, said his company was still studying how the warning would affect its advertising plans for the drug.

Dr. Feczko noted that no completed suicides had been found in any of the tests of antidepressants in the young. He said Pfizer stood behind the safety of Zoloft, the biggest-selling antidepressant.

F.D.A. officials and drug company representatives said that to provide the patient medication guides ordered by the agency, manufacturers would have to change their packaging processes entirely.

At present, most antidepressants are delivered to pharmacies in large plastic containers from which pharmacists count out pills into the familiar generic plastic vials. But in the coming months, manufacturers must instead begin delivering them in individually boxed bottles with patient guides inserted, similar to the way over-the-counter drugs like Advil and Tylenol are packaged.

Having to stock such bottles will be difficult for some pharmacies and could lead to confusion, said John Coster, a spokesman for the National Association of Chain Drug Stores. Pharmacists will have to devote considerable shelf and inventory space to storing scores of boxes of antidepressants, Mr. Coster said. And because the bottles will probably contain 30 pills each, he added, physicians will be unable to write prescriptions for, say, 20 pills or 40 pills.

"Up and down the distribution line," he said, "there's going to have to be huge adjustments."