U.S. SENATE COMMITTEE ON
Finance
SENATOR CHUCK GRASSLEY, OF IOWA - CHAIRMAN
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For Immediate Release
Friday, September 17, 2004

Grassley Urges Quick Adoption of New Warnings for Pediatric Antidepressants

WASHINGTON — Sen. Chuck Grassley has urged the Food and Drug Administration to quickly adopt the recommendations made this week by an expert advisory panel concerning the effect of antidepressants on adolescents and children and asked how the agency plans to address the matter of informed consent from parents and guardians when antidepressants were prescribed for young people.

The text of Grassley's letter to the Secretary of Health and Human Services and the Acting Commissioner of the Food and Drug Administration follows here. Grassley has been conducting oversight of the Food and Drug Administration from his position as chairman of the Senate Committee on Finance.

September 16, 2004

The Honorable Tommy G. Thompson
Secretary
Department of Health and Human Services
200 Independence Avenue, SW
Washington, D.C. 20201

Mr. Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Secretary Thompson and Commissioner Crawford:

I am pleased to note this week's very significant recommendation by its Advisory Committee that the Food and Drug Administration (FDA) should now mandate a "black box" warning about the elevated risk for suicidal behavior among children and adolescents who have been administered certain antidepressant drugs, in addition to requiring appropriate "med guides". These measures are especially critical since I also understand from previously released

studies and from the Advisory Committee's own deliberations that only one of the nine antidepressant drugs has been proven to provide any benefit to children and adolescents. In fact, in almost all cases, the FDA's own data demonstrates that these drugs actually perform no better than do placebos.

Unfortunately, the poor performance data for these drugs has been coupled with the very compelling and heart-wrenching testimony from parents and other public witnesses who identify the medications themselves as triggering tragic and unexpected suicides and suicidal behavior among users. I understand that the testimony yesterday even included discussions about patients who had not been suffering from depression, yet were prescribed these powerful drugs by physicians who may perhaps have been all too ready to medicate their patients.

I share the rather convincing opinions and concerns of the experts who have independently assessed the increased risks of suicide as a result of these drugs - especially in certain populations - and the absence of meaningful data supporting its benefits that would warrant the enhanced risks. I trust that the FDA will very quickly and fully consider the Advisory Committee's recommendations about the "black box" and "med guides", before the lives of more children are needlessly lost because parents and others lack adequate, readily understandable information when they most need it - at the precise moment when they must make critical life and death health care decisions for themselves or their loved ones. Perhaps this need for better information is best articulated by a recent letter that I received from a physician whose 15-year old son committed suicide after being on Zoloft a mere 12 days. This physician and father said:

There need to be warnings: warnings on a bottle, warnings on the product label, warnings in the package insert, warnings in the PDR. Doctors and patients need to be educated concerning the risks and warning signs. Even if it is never scientifically "proven" that the medicines actually "cause" suicide, it appears to me that there is undisputable empiric evidence that patients are, in fact, at risk. At the very least, patients and their families should be given the opportunity to discuss and be aware of these potential side effects and to take reasonable preventative measures to try to avoid these needless deaths.

As you know, suicide is the third leading cause of death among teenagers. This is a serious public health issue. For me, though, the issue is much more personal. I cannot sit idle and let this senseless tragedy happen to another family. With each day that goes by without warnings or education, other people like me will continue to lose their precious children like Josh.

Secretary Thompson and Deputy Commissioner Crawford, I want you to understand that this United States Senator also is unwilling to sit idly by and let this kind of tragedy befall other families. Moreover, I, for one, do not share the rather patronizing opinion voiced by some of the Advisory Committee members this week. Specifically, some noted that providing complete, accurate, clear and understandable information to worried parents, concerned caregivers and busy physicians will necessarily lessen the dispensing of pharmaceuticals to those patients who truly need and can benefit from them. In my judgment, better and more complete data about the very

serious risks and quite marginal documented benefits gives parents the ability to ask the right questions and arrive at the appropriate conclusions on a case-by-case basis about the best treatment for their loved ones.

Complete information will better ensure that those who most require and can potentially most benefit from these drugs will receive them - and that all of the risks and benefits have been carefully weighed and thoughtfully considered. I certainly would want to have that choice for my own children and grandchildren, and I find it difficult to imagine any caring parent or other family member would want it to be otherwise.

While the "black box" warning is a major step by the FDA, I note that the Chair of the Advisory Committee did not put to a vote another matter discussed during the meeting; that is, the issue of "signed informed consent." It is my understanding that at this time, the FDA will not require signed informed consent for the SSRIs in question. Accordingly, I am curious about the FDA's rationale for not requiring physicians who prescribe these antidepressant drugs to children to provide a clear, informed consent document that parents or guardians must read, understand and sign before accepting a prescription from their physician, as the FDA did for Lotronex. In the case of Lotronex, I understand that signed informed consent forms were required by FDA because of the risk of ischemic colitis in about 1 in 300 patients. However, in the case of antidepressants in children and adolescents, a suicide-related event involving Prozac (fluoxetine) is about 1 in 15 according to the TADS study, and about 1 in 30 for all SSRIs, according to FDA's own study.

Please note that I am not necessarily promoting that signed informed consents be required for all SSRIs; but I am wondering how the FDA intends to make the decision as to whether or not such informed consent will be required. I am asking because, as noted above, the FDA required signed informed consent for Lotronex; a drug that appears to have an adverse effect far less devastating than suicide. Although a "black box" warning and a "med guide" is a great leap in the right direction, I am troubled by the timing and direction of such warnings. I understand that the black box report warning is most often directed to the practitioner and not to the consumer. On the other hand, the "med guide" is directed to the patient, but only after the patient has left the practitioner's office. It is my understanding that an informed consent document provides current and reliable information on the risks associated with taking certain drugs, as well as the benefits documented through valid test results. While more general class information is quite useful, the informed consent documents specify the risks and benefits associated with specific drugs. Accordingly, I would appreciate knowing:

1. whether or not the FDA intends to make a determination as to the necessity for signed informed consent for SSRIs and if not, why not; and

2. the rationale for FDAs views on Lotronex risks vis a vis the risks of SSRIs, particularly when the risk of a suicide event is some ten or twenty times greater from antidepressants than it is the risk of ischemic colitis from Lotronex. I would appreciate your responses to these questions by October 18, 2004.

In the event that FDA decides to require "informed consent" despite the fact the Chair of the Advisory Committee did not bring this issue to a vote, it would seem that an informed consent form should at least need to make the following points:

"Only Prozac has been shown to be effective in treating depression in children and adolescents, and it is the only drug approved for this by the FDA;

"All other SSRIs and antidepressants have been shown to be no different than a placebo, and their use in the treatment of depression in children and adolescents is not an approved use by the FDA;

"All antidepressants increase the risk of suicidality; and

"The risk of a suicide event (planned or actually attempted) is one suicide event for every 15 to 30 children and adolescents taking the antidepressant

In closing, I am interested in hearing from the FDA about all that it is considering or planning to do concerning educating the medical community and the public about the risk-benefits of antidepressants, especially in children. Therefore, I am requesting a bi-monthly verbal or written briefing for my staff by the FDA, including any milestones, timetables, and any identified impediments that may require a legislative fix. The issue of the black box warning and the med guides are not matters that can wait months and months and I intend to keep the FDA's feet to the fire to insure that the American public is knowledgeable about the risks of SSRIs.

Thank you for your attention to this important matter.

Sincerely,

Charles E. Grassley
Chairman