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Testimony
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Anti-Depressant Use Among Children

Statement of David E. Wheadon, M.D.
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Committee on House Energy and Commerce
Subcommittee on Oversight and investigations

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Mister Chairman, Ranking Member and Members of the Committee, good morning.

Introduction

My name is Dr. David Wheadon, and I am Senior Vice President for U.S. Regulatory Affairs at GlaxoSmithKline. I appreciate the opportunity to appear before the Subcommittee today and look forward to answering your questions.

As a bit of background, I am a psychiatrist by training, and have held various positions in Clinical Development at both Eli Lilly and Company and GlaxoSmithKline, primarily focusing on central nervous system products. While at Lilly, I was involved in the development of Prozac for the treatment of depression as well as other psychiatric disorders, and have worked extensively on Paxil during my tenure at GlaxoSmithKline. In my current position, I am responsible for GlaxoSmithKline.s interactions with the FDA on all of our prescription drug and vaccine products.

I appreciate this opportunity to describe to you

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GlaxoSmithKline's continuing efforts to share information to ensure that our antidepressant paroxetine hydrochloride, known under the brand name Paxil, is used appropriately by all patients.

Background on Paxil

Paxil is a member of a class of antidepressants called selective serotonin reuptake inhibitors, or **SSRIs**. Paxil was launched in the U.S. market in 1993 for the treatment of depression in adults, also known as major depressive disorder. Since its launch, as is the case with all new drugs, we have continued to study Paxil's safety and efficacy and have sought, and received approval for, additional indications for its use. Currently, the FDA has approved Paxil and/or Paxil CR as safe and effective to treat depression, generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive compulsive disorder, pre-menstrual dysphoric disorder and posttraumatic stress disorder in adult patients. Paxil has never been licensed in North America or Europe for use in pediatric patients, and GlaxoSmithKline does not promote Paxil for use in this age group. — but did they

GlaxoSmithKline is committed to the research and discovery of medicines to improve human health and fill unmet medical needs. The unmet need in child and adolescent depressive and anxiety disorders is substantial; the consequences of not adequately recognizing and treating such disorders include significant morbidity, disability and indeed death. Suicidal behavior, suicide attempts and completed suicide can all be extremely unfortunate complications of childhood and adolescent depression. We have studied Paxil in pediatric patients who suffer from depression, obsessive compulsive disorder and social anxiety disorder. We conducted eight major safety and efficacy trials, and one pharmacokinetics study. Seven of these studies were conducted under an Investigational New Drug application with the FDA, and the other two were conducted under similar applications in Canada or France.

Complexity of Depression

As a psychiatrist, I would like to take a moment to talk about some unique characteristics of depression and similar psychiatric disorders. Depression is a complex and devastating disease, and one of its cardinal symptoms is suicidality -- defined as suicidal thinking, suicide attempts, or completed suicides. It is well recognized that suicide can be a tragic outcome of depression, and it is one of the leading causes of death among young people. According to researchers supported by the National Institute of Mental Health, among adolescents who develop major depressive disorder, as many as 7% may commit suicide in their

young adult years. Tragically, suicide is the third leading cause of death among young people.

Although most antidepressants are not approved for use in the pediatric population, physicians sometimes will prescribe these drugs to depressed children ..off-label... We are aware that prescriptions have been written for children for the various products represented by the companies here today, that may or may not be indicated for their use. It is important to recognize that the increased use of antidepressants among children 10-19 years of age has been accompanied by a decrease in the suicide rate in this age group. According to a study published in the Archives of General Psychiatry in October 2003, for each 1 percent increase in the use of **SSRIs** among adolescents, there was a decrease of 0.23 suicides per 100,000 adolescents per year. Although this is an epidemiologic association that does not necessarily prove cause-and-effect, it does suggest that we as a society are beginning to recognize and appropriately treat depression in children and adolescents.

While physicians have found antidepressants to be useful in treating pediatric patients with depression, these drugs have historically been very challenging to study in clinical trials. Not only is demonstration of efficacy a challenge due to the particularly high placebo-response rates in pediatric depression, but evaluation of safety and tolerability is confounded by the fact that cardinal symptoms of the disease such as anxiety, sleep disturbance and suicidality may masquerade as side-effects of treatment. It is precisely for this reason that the symptom complex of suicidal thinking, suicide attempts, and completed suicides -- which we refer to as suicidality -- is particularly difficult to assess in antidepressant clinical trials. Not all acts of self-destructive behavior often seen in adolescents are associated with real suicidal intent. GSK.s meta-analysis of the pediatric clinical trial data described below utilized an algorithm approach, evaluating adverse event reports and classifying them as ..possibly suicide-related.. and/or as a ..suicide attempt... This could be imprecise; for example, one classification of ..suicidality.. in one of our trials consisted of a subject slapping her face.

Paxil is an effective and generally well-tolerated drug for adults with depression and other psychiatric disorders. Given the unmet medical need in children and adolescents with depression, GlaxoSmithKline undertook to study Paxil in pediatric populations in the hope that it might help some of these young patients. Our

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three trials in pediatric depression as a group did not, however, provide sufficient evidence that Paxil is more effective than placebo, although we did see some signs of efficacy in our first pediatric depression trial. It is important to note that even for known effective, approved antidepressants, 4 out of 10 studies failed to demonstrate efficacy because of the high placebo response rates seen in these studies. Given those statistics, we were encouraged by the results of our first trial.

One possible explanation for the outcome of our pediatric depression trials was the high placebo response rate, which made it difficult for the drug to show statistically significant efficacy. Our trials showed a high response rate to Paxil but also a high response rate to placebo -- as is common in clinical trials for depression -- so it was difficult to demonstrate a statistically significant difference between the two. Another impediment to measuring efficacy in the pediatric population is the need for more refined scales for measuring antidepressant efficacy in this population.

Of note, in our studies of pediatric patients with obsessive-compulsive disorder and social anxiety disorder, Paxil did demonstrate statistically significant evidence of efficacy.

Communication of Results

GlaxoSmithKline.s policy is to ensure transparency of the clinical data the company collects on its marketed medicines. Specifically, we endorse the principles of our trade association, the Pharmaceutical Research and Manufacturers of America, also known as PhRMA, that call for timely publication of meaningful trial results. In fact, we helped to draft the PhRMA principles.

Although we were not able to demonstrate efficacy in pediatric depression, data from clinical trials was shared with the healthcare community. Over the past six years or so, data from the pediatric depression studies has been communicated through peer-reviewed journals, poster presentations at scientific meetings, and medical letters to health care professionals -- all of which are accepted standard practices for making data available to prescribers. A bibliography of publications and posters derived from these studies was posted to the GlaxoSmithKline corporate website on June 14, 2004.

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As for our safety data concerning suicidality in pediatric patients treated with Paxil, I should first point out a few

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issues that seem to get lost in the discussion surrounding the pediatric use of antidepressants. Firstly, not a single person committed suicide in any of our pediatric trials, which included over 1,000 patients treated with Paxil. Secondly, we did not see a statistically significant signal of increased suicidality in any of the trials individually. However, when, as part of our standard internal process of continuing ongoing safety reviews, we combined and performed analyses on all nine completed studies together -- the meta-analysis -- we did see a possible signal, primarily in adolescent patients with depression. On completion of those analyses in 2003, GlaxoSmithKline proactively sought the advice of external experts and regulatory agencies including the FDA. The FDA promptly issued a Talk Paper and brought this issue to the attention of the medical community and the public in June 2003. Thirdly, it is important to note that the possible signal of suicidality seen in the adverse event data was not confirmed by analysis of the data from the depression rating scales. In all of our depression studies, the depression rating scales used contained a ..suicidality.. question, a physician rated score of suicidality. Analysis of this data showed no signal of suicidality associated with Paxil in pediatric patients.

The FDA is in the midst of further considering this issue, recognizing that any such review must be done thoroughly and be guided by the best scientific and clinical research that exists. Thus, we welcome the FDA's approach of asking researchers at Columbia University to undertake an independent evaluation of the data on all antidepressants, including **SSRIs**. As I am sure you are all aware, the agency will convene a meeting of experts next week to review the outcome of this evaluation. Given the complexity of this matter, we believe the FDA's approach has been appropriate.

Concurrent with this review and with our support, the FDA has required a new warning on all products in the newer antidepressant class, including Paxil. This new labeling expands upon -- and gives more prominence to -- language regarding the disease-related risk of suicidality that has been in antidepressant labeling for many years. Both the new and old language reflect the phenomenon that, during early treatment and recovery, symptoms such as lack of energy and motivation may improve ahead of depressive and suicidal thinking. The possible consequence of this is that these still-depressed patients may now have the energy and motivation to act on their suicidal thoughts. The new language underscores the need for physicians and family members to observe the patients for worsening depression or signs of suicidality -- whether or not they are taking antidepressants. We support this new warning, and we have

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included it in our labeling.

Finally, as noted above, in the interest of full transparency, and because we feel it is important to clarify the data related to GlaxoSmithKline.s clinical trial results regarding Paxil in **children** and adolescents, on June 14, **2004**, we took the unprecedented and extraordinary step of providing access via our website to the clinical trial reports and other information about Paxil data in **children** and adolescents. We hope this information will be useful and informative to all those who access it.

Clinical Trial Register

It has been the practice of GlaxoSmithKline to communicate to the medical community safety and efficacy data from our clinical trials through posters and abstracts presented at medical conferences, through peer-reviewed journal articles, and through medical information letters provided to physicians upon request.

GlaxoSmithKline has also recently taken the additional step in on-line access to clinical trial information by beginning to put study summaries of our marketed pharmaceutical products on a single Internet site accessible to physicians and the public. The database, called the GlaxoSmithKline Clinical Trial Register, provides summaries of trial protocols and corresponding results for GlaxoSmithKline-sponsored trials of marketed medicines. In addition, the register provides citations to publications that have appeared in the medical literature. Just last week we began posting data for our antidiabetic Avandia - one of the company.s most important products - and we will begin posting summaries for other products in the near future.

This Clinical Trial Register had been under consideration and development for several months. Our company acts in the interests of physicians and patients, and we will take whatever measures are necessary to maintain their trust.

Of course, we will also continue to communicate clinical data in journals, at scientific meetings, and in letters to healthcare professionals. It is also important to emphasize that while we are pleased that we will be able to provide this clinical data online, it is the prescribing information approved by regulatory agencies that must continue to guide the appropriate use of our medicines.

Conclusion

We strongly believe that GSK acted appropriately in analyzing, interpreting and communicating data from Paxil trials in children and adults given the information available at any given time over the last 11 years.

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Thank you for your time. I look forward to answering any questions you may have.

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