Lilly Comments on NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Fluoxetine

The draft report of the NTP-CERHR Expert Panel on the Reproductive and Developmental Toxicity of Fluoxetine was recently issued for public comment The topics summarized in this draft report are consistent with previous reports from NTP-CERHR evaluating environmental chemicals. While the overall summary, conclusions, and list of critical data needs have not yet been written, summaries and conclusions have been drafted for the sections on developmental toxicity and reproductive toxicity.

Comments by Eli Lilly and Company on the draft report of the NTP-CERHR Expert Panel can be summarized as follows:

1. There is not sufficient evidence to conclude that fluoxetine results in developmental toxicity manifested as poor neonatal adaptation or reduced size of breastfed infants.
2. Beneficial or unwanted side effects of SSRIs on sexual performance appear to be reversible and any risks should be evaluated by patients and their physicians. Since any effects on sexual performance from the use of SSRIs are confounded by the disease state and appear to be based on reversible pharmacology, fluoxetine should not be classified as a reproductive toxin in humans.
3. Fluoxetine is only available through prescription, so the benefits and potential risks of use should be evaluated on a case-by-case basis by patients and their physicians.

1. Developmental Toxicity of Fluoxetine

According to the Expert Panel,

> *…there is sufficient evidence in humans to determine that prenatal exposure to fluoxetine results in developmental toxicity in the form of poor neonatal adaptation (e.g., jitteriness, tachypnea, hypoglycemia, hypothermia, poor tone, respiratory distress, weak or absent cry, or desaturation on feeding) at typical therapeutic exposures (20–80 mg/day orally) during the third trimester of pregnancy.*

In addition, the Expert Panel stated:

> *The evidence is sufficient to demonstrate that exposure to fluoxetine through breast milk can result in reduced size of infants.*

Eli Lilly and Company does not believe that there is sufficient evidence to support a conclusion that fluoxetine results in developmental toxicity manifested as poor neonatal adaptation or reduced size of breastfed infants. The Expert Panel and the authors of the

cited publications did not fully consider the confounding effects of underlying maternal depression leading to poor pregnancy outcomes when evaluating the results of the research.

Poor Neonatal Adaptation

The Expert Panel appears to have based this conclusion on the work of Chambers et al. (1996). The Expert Panel noted some weaknesses in this report, including a small number of subjects and models that have many covariates (due to confounding factors such as smoking, alcohol consumption, use of other psychotherapeutic medications, and differences in maternal age). Other epidemiologists consider the study conclusions to be limited precisely because of these confounding factors (Llewellyn et al., 1997).

Weaknesses of the study by Chambers et. al (1996) have been summarized by Wisner et al. (1999) and Robert (1996). Probably the most significant weakness of this study was that the control group does not allow separation of fluoxetine effects from those of the underlying maternal depression. The control group for the study by Chambers et al. (1996) consisted of pregnant women who called the California Teratogen Information Service and Clinical Research Program with questions about drugs and procedures not considered to be teratogenic. This control group had a lower incidence of confounding factors than the fluoxetine treatment groups. There was no assessment of the incidence of untreated depression in the control group. Fluoxetine was used either early in pregnancy (exposed-early treatment group) or throughout pregnancy for most of the rest of the women (exposed-late treatment group). Comparison between the exposed-early group and the exposed-late group led Chambers et al. (1996) to conclude that exposure to fluoxetine in late pregnancy increases the risk of poor neonatal adaptation. This finding might also be explained by the fact that severe depression could have required treatment throughout pregnancy in the exposed-late group (Robert, 1996). The exposed-early group may have had a mild form of depression, allowing treatment with fluoxetine to be stopped. From this study, there is no way to determine if the results represented the effects of the underlying severity of the disease and maternal condition or long-term exposure to fluoxetine. Chambers et al. (1996) acknowledged that the "extent to which these findings may be due to the underlying maternal condition is unknown."

The risks of untreated depression may include poor nutrition, disrupted sleep patterns, difficulty following medical and prenatal care recommendations, suicide, worsening of co-morbid medical illness, and increased exposure to tobacco, alcohol, or drugs (Llewellyn et al., 1997). Maternal depressive symptoms can also lead to prematurity and low birth weight (Orr and Miller, 1995; Steer et al. 1992). Preterm birth can be associated with postnatal complications. Clearly, without treatment for depression, pregnant women and their infants can face significant health risks. Even with antidepressant treatment, the severity of depression and maternal condition can complicate the interpretation of results from studies like those of Chambers et al. (1996).

Reduced Size of Breastfed Infants

This second conclusion appears to be primarily based on the presence of fluoxetine in breast milk and the results in another report by Chambers et al. (1999), which evaluated weight of breastfeeding infants. Chambers et al. (1999) indicates "that infants who are breastfed by mothers who take fluoxetine track a growth curve significantly below that of infants breastfed without medication." Fluoxetine levels were not actually measured in breast milk by Chambers et al. (1999), but infant exposure was assumed to have occurred from breastfeeding. They did note, however, that the possibility of direct effects of fluoxetine on weight gain in nursing infants is not supported by the dose they could have received. Less than 10 percent of a maternal dose of fluoxetine is transferred to a nursing infant (Taddio et al., 1996). Chambers et al. (1999) also acknowledged "women with an underlying condition requiring a psychotherapeutic medication may breastfeed less often and engage in other behaviors that influence postnatal weight gain in their infants."

The Expert Panel identified the Chambers papers (1999, 1996) as the "most complete" and "well designed" studies supporting their conclusions of a relationship between maternal fluoxetine exposure resulting in poor neonatal adaptation and reduced infant size. However, neither of the Chambers papers controlled for confounding similar outcomes resulting from underlying depression in the treated women. For this reason, Eli Lilly and Company does not believe there is sufficient evidence to conclude that maternal fluoxetine exposure results in developmental toxicity in humans.

2. Reproductive Toxicity of Fluoxetine

According to the Expert Panel,

> *…there is sufficient evidence in humans that fluoxetine produces reproductive toxicity in men and women manifested as impairment of sexual performance, especially orgasm.*

The Expert Panel also noted that effects on individual sexual performance are unpredictable. Depression is associated with impaired sexual function, and successful treatment of depression may be associated with improvements in sexual function. Some evidence does suggest that SSRIs can cause untoward sexual experiences. At least one report indicates that improvement in sexual function (reversal of sexual dysfunction) occurs when the dose of an SSRI is diminished or the drug is withdrawn (Montejo-Gonzalez et. al, 1997). Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, the product information for fluoxetine recommends that physicians should routinely inquire about such possible side effects with their patients. Important to note is that sexual performance is not necessarily equivalent to reproductive performance. Since any effects on sexual performance from the use of SSRIs are confounded by the disease

state and appear to be based on reversible pharmacology, fluoxetine should not be classified as a reproductive toxin in humans.

3. Risk/Benefit Considerations in the Use of Fluoxetine

Subpopulation of patients: Children

The U.S. Food and Drug Administration recently approved Prozac® (fluoxetine hydrochloride) for the treatment of major depressive disorder and obsessive-compulsive disorder in the pediatric population. The clinical data reviewed by the FDA indicate that Prozac 20 mg has a comparable profile of safety and efficacy in both adults and children. Eli Lilly and Company submitted four pediatric studies: two clinical studies for depression, one for obsessive-compulsive disorder, and one pharmacokinetic study. The FDA based its decision on placebo-controlled clinical trials.

Lilly is working closely with the FDA on the design of a Phase IV post-marketing study to further evaluate whether there is any long-term effect on either weight or height of children who take Prozac. The FDA stated in its announcement that "the clinical significance of height and weight differences on long-term growth is unknown." (www.fda.gov) The Phase IV studies should help provide additional information in this area. Nonetheless, the FDA has found the product to be both safe and effective as seen in its approval.

On December 10, 2003 the MHRA (Medicines and Healthcare Products Regulatory Agency) announced, “On the basis of a review of the safety and efficacy of the SSRI class in the treatment of pediatric major depressive disorder undertaken by the Expert Working Group of the Committee on Safety of Medicines (CSM), the CSM has advised that the balance of risks and benefits for the treatment of major depressive disorder in under 18s is judged to be unfavorable for sertraline, citalopram and escitalopram and unassessable for fluvoxamine. Only fluoxetine (Prozac) has been shown in clinical trials to have a favorable balance of risks and benefits for the treatment of MDD in the under 18s”. (www.mhra.gov.uk)

General Patient Population

The stated purpose of the NTP-CERHR is to address the “widespread concern among health professionals, environmental scientists, and the public that environmental exposures may be contributing to human reproductive and developmental disorders”. The chemicals previously reviewed by the NTP-CERHR reach the general population through environmental exposure. Some of these chemicals have the potential for a health risk, with no potential for a health benefit. The result of exposure of individuals is certainly not monitored by a health care professional.

Unlike the chemicals that can reach entire populations by environmental exposure, fluoxetine is available only through prescription. Individuals are monitored by physicians qualified to evaluate the potential benefits and risks of fluoxetine to their patients. All of the approved uses of fluoxetine have been evaluated by the U.S. Food and Drug Administration.

Product information that describes potential benefits and risks of fluoxetine has been made available to physicians and the public. For example, the presence of fluoxetine in breast milk is noted in the product information and nursing is not recommended. It is also noted in the product information that fluoxetine should only be used during pregnancy, labor and delivery if the benefit justifies the potential risk. Determining the potential for certain developmental or reproductive hazards from the use of fluoxetine is complicated by the same hazards resulting from maternal depression. Improvement in depression from the use of fluoxetine might reduce the risk of these hazards. This risk/benefit consideration is best made on a case-by-case basis by physicians and their patients.

References

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