

AN OVERVIEW OF PAXIL, PREGNANCY AND BIRTH DEFECTS

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HISTORY

Since its introduction into the world of depression, Paxil has generated a healthy dose of controversy and publicity. There are those who claim it to be effective and others who believe it to be nothing more than a placebo.¹ The Food and Drug Administration (FDA) approved the drug to be sold in the United States in December of 1992, after initially being launched in the United Kingdom a year before under the name Seroxat.² Manufactured by GlaxoSmithKline (GSK), formerly SmithKlineBeecham, Paxil was touted as the magic pill that would change the lives of depressed people everywhere. GSK began selling its control release formula of Paxil, marketed as Paxil CR, in April 2002.³

Paxil is the trade name for Paroxetine Hydrochloride and is included in a class of medicines called selective serotonin reuptake inhibitors (SSRIs).⁴ Certain brain chemicals called neurotransmitters, including serotonin, are associated with depression. Research suggests that abnormalities in neurotransmitter activity affect mood and behavior.⁵ SSRI drugs seem to relieve symptoms of depression by blocking the reabsorption or reuptake of serotonin by certain nerve cells in the brain. Hence, more serotonin is in the brain which enhances neurotransmission, or the sending of nerve impulses, and improves mood.⁶ Consequently, SSRIs are popular for treatment of depression, anxiety disorders, and some personality disorders.

GSK marketed Paxil to treat depression, panic disorder, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder and generalized anxiety disorder.⁷ Paxil CR not only covered those social afflictions but was also promoted to women as effective treatment for premenstrual dysphoric disorder (PMDD)⁸. PMDD is

¹ Irving Kirsch et al., (2008) *Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration*. PLoS Med 5(2): e45 doi:10.1371/journal.pmed.0050045 (last visited April 15, 2008).

² Prescription Drug Product List – 16th Edition at <http://www.fda.gov/cder/rxotcdol/pdp1596.htm> (last visited April 15, 2008).

³ Paxil CR at <http://www.gsk.com/investors/reports/halfyear2002/busrev.htm> (last visited June 25, 2009).

⁴ Paroxetine at http://www.nci.nih.gov/Templates/db_alpha.aspx?CdrID=45553 (last visited June 25, 2009)

⁵ Selective Serotonin Uptake Inhibitors at <http://www.mayoclinic.com/health/ssris/MH0006> (last updated December 10, 2008)

⁶ See supra

⁷ Paxil Prescribing Information at http://us.gsk.com/products/assets/us_paxil.pdf (last visited June 25, 2009).

⁸ Paxil Prescribing Information at http://us.gsk.com/products/asstes/us_paxil_cr.pdf (last visited June 25, 2009)

similar to pre-menstrual syndrome except that symptoms are more severe and debilitating.⁹

WITHDRAWAL SYNDROME and SUICIDE

While GSK was busy making money hand over fist through the sales of its drug and creating different disorders for which to market Paxil, it was discovered that adequate warnings were not given regarding a variety of potentially severe and fatal side effects. By 1997, Paxil had already generated \$1 billion in sales and for obvious reasons GSK did not want to lose money on its drug.¹⁰ In 2001, BBC news in the United Kingdom reported people were suffering withdrawal symptoms when trying to discontinue Paxil and the World Health Organization reported it was the hardest to stop taking out of all antidepressants.¹¹ This drew attention to the fact that patients stayed on Paxil not because they needed it, but because they had become addicted to it. GSK knew this was a risk, yet chose not to include it in the warnings label until pressured by the FDA.¹² In 2003, the FDA began reviewing reports of a possible increased risk of suicidal thinking and suicide attempts in children and adolescents.¹³ Again, GSK knew this and looked the other way. After much pressure from the FDA, GSK ultimately changed the Paxil label to include a black box warning to indicate children, adolescents and young adults are at a higher risk of suicide behavior and suicidal thinking.¹⁴ Litigation related to Paxil and increased suicidal tendencies is ongoing.

PREGNANCY and BIRTH DEFECTS

Paxil also causes certain types of birth defects in those babies whose mothers ingested Paxil while pregnant. Internal documents show GSK knew this was a potential risk in the mid 1990s and decided making money was more important than women having healthy babies. In fact, when first put on the market in 1993, Paxil was classified as a Category B drug on the warning label – meaning it was shown to be safe for pregnant women to take.¹⁵ In 1996, the FDA requested all drug companies that manufactured SSRIs to change their pregnancy categories to a C. GSK then changed Paxil to a Category D in December 2005, which is a more severe category and essentially

⁹ Premenstrual Dysphoric Disorder at <http://www.nlm.nih.gov/medlineplus/ency/article/007193.htm> (last updated December 31, 2008).

¹⁰ Greg Fisher et al., (December 9, 2004) *Drug Maker Withheld Paxil Study* at <http://abcnews.go.com/Health/Story?id=311956&page=4> (last visited April 15, 2008)

¹¹ Anti-Depressant Addiction Warning at <http://news.bbc.co.uk/2/hi/health/1382551.stm> (last visited June 25, 2009).

¹² Tonks, Bristol, *Withdrawal from Paroxetine can be Severe, Warns FDA*, *BMJ* 2002; 324 (7332): 260 (2 February) at <http://bmj.com/cgi/content/full/324/7332/260> (last visited April 15, 2008).

¹³ FDA Patient Safety News: Show#18, August 2003 at <http://www.accessdata.fda.gov/psn/printer-full.cfm?id=22> (last visited June 25, 2009).

¹⁴ See *supra* note 2

¹⁵ Labeling at <http://cfr.vlex.com/vid/201-57-content-labeling-prescription-19708611> (last visited June 25, 2009).

means that studies in pregnant women have shown a risk to the fetus.¹⁶ Of note, Paxil is the only SSRI to have a Category D classification.¹⁷

In 2005, two very important studies were publicized that drew attention to the risk of pregnant women ingesting Paxil. One was actually a retrospective study by GSK using United Healthcare data. In that study almost 6,000 infants of mothers who were given Paxil or other antidepressants were evaluated. The study indicated women who ingest Paxil while pregnant are at a higher risk of having a baby with a cardiac defect and/or congenital malformation than those pregnant women who do not. It showed a 1.5% increased risk for cardiovascular malformations compared to other antidepressants and the prevalence of all congenital malformations was 4% for Paxil as opposed to 2% for other antidepressants.¹⁸

The second study, which was not published in the United States, showed a two-fold increase in cardiac defects as compared to the general population. Data from the Swedish Medical Birth Registry was used to compare pregnant women who were exposed to SSRIs in early pregnancy. Basically, the author studied the statistics on all births from July 1, 1995 – 2003 and discovered a higher incident rate of cardiovascular defects in those babies whose mothers ingested Paxil compared to the entire registry population.¹⁹

Both studies showed exposure to Paxil in the first trimester of pregnancy may be associated with an increased risk of cardiac defects, specifically atrial and ventricular septal defects, which are holes in the walls of the chambers of the heart. Holes in the heart are the most common form of defect to be associated with the ingestion of Paxil and if they do not close up on their own or are large in size, surgery may be necessary. Some other defects attributable to Paxil are Transposition of the Great Arteries (TGA), Tetralogy of Fallot (TOF), Craniosynostosis and Omphalocele.^{20,21}

Transposition of the Great Arteries occurs when the two main arteries, the aorta and pulmonary artery, leaving the heart are reversed. These two arteries are connected to the incorrect chambers of the heart and this changes the way the blood circulates through the body. As a result there is a shortage of oxygen in blood flowing from the heart to the rest of the body and the body can not function properly.²² Tetralogy of Fallot has four key defects: a large ventricular septal defect, pulmonary stenosis, right ventricular

¹⁶ See *supra*

¹⁷ ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 92, April 2008. *Use of Psychiatric Medications During Pregnancy and Lactation*.

¹⁸ *Epidemiology Study: Bupropion in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformation. Study No. EPI083*. Ingenix, A UnitedHealth Group Co; September 2005

¹⁹ Kallen B. *Letter to the Editor: Antidepressant Drugs During Pregnancy and Infant Congenital Heart Defect*. *Reproductive Toxicology* 2006; 21:221-222

²⁰ Carol Louic Sc. D, et al., *First-Trimester Use of Selective Serotonin-Reuptake Inhibitors and the Risk of Birth Defects*. *N Engl J Med* 356; 26:2675-2683 (2007)

²¹ Sura Alwan, et al., *Use of Selective Serotonin-Reuptake Inhibitors in Pregnancy and the Risk of Birth Defects*, *N Engl J Med* 356; 26:2684-2692 (2007)

²² *Transposition of the Great Arteries* at <http://www.mayoclinic.com/health/transposition-of-the-great-arteries/DS00733> (last modified May 8, 2006).

hypertrophy and an overriding aorta. Together, the four defects mean the lungs do not receive enough oxygen because of poor blood flow and oxygen-poor blood flows out to the body.²³ Both TGA and TOF must be treated surgically. Craniosynostosis results because of premature fusion of one or more cranial sutures (skull bones), often resulting in an abnormal head shape. Depending on the severity, surgery is an option to correct the craniosynostosis.²⁴ Omphalocele is a congenital birth defect in which the muscles in the abdominal wall do not close properly resulting in the intestines remaining outside the umbilical cord. Surgery is required to correct it.²⁵

Because of the conclusions in the two studies, in September 2005, GSK issued a “Dear Doctor” letter to healthcare providers. The letter stated GSK was changing its label with respect to Paxil during pregnancy to provide a stronger warning. It would indicate for the first time that there could be a connection between Paxil and birth defects.²⁶ In December of 2005, the FDA issued an alert advising that study results suggested that taking Paxil during the first three months of pregnancy increases the risk for birth defects, particularly heart defects and that GSK had changed Paxil’s pregnancy category to a “D” and added new data and recommendations to the Warning section for prescribing information.²⁷

In addition to the birth defects caused by Paxil, in February of 2006, the New England Journal of Medicine published a study in which it concluded that babies exposed to SSRI antidepressants in the last trimester were six times more likely to develop Persistent Pulmonary Hypertension of the Newborn (PPHN) than those who were not exposed.²⁸ PPHN is a serious and life-threatening lung condition that occurs after birth of the newborn. Babies with PPHN have high pressure in their lung blood vessels and are not able to get enough oxygen in their bloodstream. It occurs because the newborn’s circulation system does not adapt to breathing outside the womb. About one to two babies per 1,000 babies born in the U.S. develop PPHN shortly after birth, and they often need intensive medical care such as oxygen, assisted ventilation, nitric oxide, and high frequency oscillatory ventilation.²⁹ As a result of the Chambers study, in July 2006, the FDA issued another alert and stated there was an increased risk in PPHN for infants

²³ *Tetralogy of Fallot* at http://www.nhlbi.nih.gov/health/dci/Diseases/tof/tof_what.html (last updated December 2007)

²⁴ *NINDS Craniosynostosis Information Page* at <http://www.ninds.nih.gov/disorders/craniosynostosis/craniosynostosis.htm> (last updated Feb. 12, 2007).

²⁵ *Omphalocele* at <http://nlm.nih.gov/medlineplus/ency/article/000994.htm> (last updated Oct. 8, 2007).

²⁶ *Letter to Healthcare Professionals from GlaxoSmithKline* (September 2005) at http://www.fda.gov/medwatch/SAFETY/2005/Paxil_dearhcp_letter.pdf

²⁷ *FDA Public Health Advisory Paroxetine* (December 8, 2005) at <http://www.fda.gov/cder/drug/advisory/paroxetine200512.htm>

²⁸ Christine D. Chambers Ph.D, et al, *Selective Serotonin-Reuptake Inhibitors and Risk of Persistent Pulmonary Hypertension of the Newborn* N. Eng J Med 354:6:579-587 (2006)

²⁹ Robin H. Steinhorn, MD *Pulmonary Hypertension, Persistent-Newborn* at <http://www.emedicine.com/ped/topic2530.htm> (last updated Apr 19, 2007).

whose mothers took SSRIs.³⁰ It stated being on Paxil after the twentieth week increases the risk to between six and twelve births for every 1,000.³¹

LITIGATION

Based on the results of both the unpublished and published studies evaluating babies whose mothers were on Paxil or other SSRIs, there is strong evidence to conclude GSK manufactured a drug that caused babies to be born with cardiovascular defects and/or congenital malformations. Furthermore, GSK knew the risk existed before 2005 and did not warn the public of such a potentially severe and fatal consequence of taking its drug.

At the time of submission of this paper, several hundred birth defects cases have been filed nationwide. The majority have been filed in the Court of Common Pleas in Philadelphia, Pennsylvania as GSK's offices are located there. Cases have also been filed in other states around the country based on client's residence and/or generic manufacturer and a few have also been filed in federal court.

Cases have been set for trial in Philadelphia, PA beginning in the Fall of 2009. There are also trial settings in California, Missouri and Illinois. Depositions are underway of key GSK employees and discovery related to case specific issues is ongoing.

³⁰ *FDA Alert: Increased Risk of Neonatal Persistent Pulmonary Hypertension* (July 2006) at <http://www.fda.gov/cder/drug/infoSheets/HCP/paroxetineHCP.htm>

³¹ *See supra*