

October 21, 2009

Mr. Akira Nagatsuma, Minister of Health, Labour, and Welfare
Marc Dunoyer, President GlaxoSmithKline

Yakugai Ombudsperson
Medwatcher Japan
Toshihiro Suzuki, Representative

AM Bldg. 4th Floor, 1-14-4 Shinjuku,
Shinjuku-shu, Tokyo 〒162-0022
Tel.: 03(3350)0607
FAX 03(5363)7080
E-mail: yakugai@t3.rim.or.jp
URL: //www.yakugai.gr.jp

Demand Regarding Use of Antidepressant Paxil Tablets in Pregnant Women

I. Purpose of the Demand

1. Revision of Package Insert and Need of Information leaflet for Patient

We demand that the Warnings section of the package insert should be revised to include at least following four issues and, that the information leaflet for patient should be provided at medical practice in order to call sufficient attention to cardiac malformations, drug withdrawal syndrome and persistent pulmonary hypertension in newborns as a result of treatment with the antidepressant Paxil during pregnancy.

- (1) That there is a high risk of congenital anomalies, particularly cardiovascular disorders (primarily ventricular septal defects and atrial septal defects), drug withdrawal syndrome in newborns and persistent pulmonary hypertension of the newborn delivered by women treated with Paxil in pregnancy

- (2) That treatment should be discontinued or replaced with alternative treatment when patients being treated with Paxil become pregnant unless continuing treatment is clearly therapeutically justified
- (3) That women who are pregnant or child-bearing age should not, as a general rule, take this medication, and should not start treatment unless no alternative treatment is available
- (4) When Paxil is used, the patient's informed consent should be obtained after a full explanation of the dependency and the risk of congenital anomalies in newborns

2. Establishment of Fact-Finding Research Group

We demand the establishment of a research group to look into the facts concerning the use of the antidepressant Paxil in pregnant women as well as the facts concerning cardiac malformations in newborns when pregnant women are treated with Paxil.

II. Reason for the Demand

1. Summary of Paxil Tablets

Paxil antidepressant tablets (generic name: paroxetine hydrochloride) are a type of SSRI (selective serotonin reuptake inhibitor) which came out on the market in November 2000 in Japan and are now widely used as an antidepressant. It became the top-earning antidepressant in the Japanese market (50 billion yen) in 2007.¹ The dosage forms in Japan are the 10 mg and 20 mg tablets, and are indicated for "depression, depressed state, panic disorder, and obsessive compulsive disorder."²

2. Objective Evidence of Teratogenicity and Persistent Pulmonary Hypertension

As noted below and shown in the research report by D.Healy and D.

Mangin (Attachment 1), and the report by R. Hama (Attachment 2), it is now evident that the use of Paxil tablets (referred to below as "Paxil") during pregnancy involves the risk of "teratogenicity," that is, congenital anomalies in fetuses and persistent pulmonary hypertension of the newborn (PPHN).

(1) Results of Epidemiological Study

- 1) The FDA analyzed two unpublished epidemiological studies, and issued the following advisory concerning the teratogenicity of Paxil in December 2005.³
 - (i) In a study using Swedish national registry data, women who received Paxil in early pregnancy had an approximately 2-fold increased risk for having an infant with a cardiac defect compared to the entire national registry population (the risk of a cardiac defect was about 2% in Paxil-exposed infants vs. 1% among all registry infants).
 - (ii) In a separate study using a United States insurance claims database, infants of women who received Paxil in the first trimester of pregnancy (up to the 14th week) had an approximately 1.5-fold increased risk for cardiac malformations and an approximately 1.8-fold increased risk for congenital malformations overall compared to infants of women who received other antidepressants. The risk of a cardiac defect was 1.5% in Paxil-exposed infants vs. 1% among infants exposed to other antidepressants.
 - (iii) Most of the cardiac defects were atrial or ventricular septal defects.

- 2) A meta-analysis of epidemiological data on the risk of congenital malformations during the use of Paxil in the first trimester of pregnancy is available on the clinical study registry system of GlaxoSmithKline, the manufacturer and distributor of Paxil.

According to the results, a total of 15 studies comprising 12 cohort studies (two of which are (i) and (ii) above) and three case-control studies indicated that the risk for congenital malformations is 1.3 times greater and the risk for cardiac malformations is 1.5 times greater when Paxil is used.⁴

- 3) A retrospective case-control study in which 377 women whose infants were born with PPHN and 836 women whose infants were

born healthy indicated that risk of PPHN was increased , approximately 6 times greater, in the infants delivered by women who had administered SSRI after 20 th week of gestation.⁵

(2) Matters Pointed Out in Japanese Review Report

The materials⁶ attached to the Review Report⁷ in Japan also include results suggesting the effect of Paxil on fetuses. Specifically, rat fertility and general reproductive studies conducted as part of reproductive toxicity revealed effects such as increase in disability of mating and fertility, increase in mortality of parent rat and post-implantation, lower birth weight, and dose-dependent decrease in 4-days survival of newborns. Additional studies also revealed the male's lower fertility and injuries induced in male's reproductive organs. As noted in investigational report by R.Hama (Attachment 2), Paxil had been found to result in reproductive toxicity at the approval review stage.

However, the Review Report merely comments that "*in view of the reproductive toxicity profile (see Section II), the Precautions state that 'Paxil should not be given unless it is determined that the therapeutic benefits outweigh risks (the safety of treatment during pregnancy has not been established)'*," and the risks posed by Paxil to fetuses cannot be said to have been adequately reviewed.

(3) Case Reports of Adverse Drug Reactions in Japan

No epidemiological study such as those noted in section (1) has been conducted in Japan, but 4 cases of atrial septal defects and 3 cases of ventricular septal defects were reported as adverse drug reactions of Paxil to the MHLW from 2000 to 2008.⁸

The package insert for Paxil tablets state merely *that the results of overseas epidemiological studies showed an increased risk for congenital anomalies, especially cardiovascular abnormalities, in newborns*, yet it is clear that cardiovascular abnormalities have also occurred in Japanese newborns, as found in the above case reports of adverse drug reactions to the MHLW(incidentally, MHLW has received no reports of such ADR with Fluvoxamine (proprietary name: Luvox, Depromel), which is another SSRI, or Milnacipran (proprietary name:

Toledomin), which is an SNRI, or the like).

3. Objective Evidence of Withdrawal Symptoms

It has also been pointed out that patients become dependent on SSRI's, including Paxil tablets, and undergo withdrawal upon discontinuing medication. This is an important point in reviewing the use of Paxil in pregnant women as well as patients with child-bearing age.

(1) Statements in the Review Report

The following is stated first on the issue of withdrawal in the section entitled "2) Safety" in the "Overview of the Review by the Review Center" of the Review Report⁷ detailing the results of the approval review: "*(v) Effects of Discontinuing Treatment: No data on the effects of discontinuing treatment have been obtained in Japan, but abrupt discontinuation of SSRI's, including Paxil, has been known in rare cases to lead to withdrawal syndrome, including dizziness, head ache, insomnia, malaise, exacerbation of anxiety, agitation, queasiness, and sensation disorders (overseas references). As a result, the Precautions describe symptoms and measures that should be taken when treatment is discontinued.*"

The Review Report No2 also stated in "*(g). Data on Clinical Study Results*" that the sponsor "*was asked to compile data on the dependency and withdrawal associated with Paxil, and responded that, based on analysis of the preclinical and clinical safety database, the primary symptom was dizziness, there was no difference in the types of withdrawal symptoms regardless of treatment period, severity was mild to moderate, and problems could be prevented by gradually reducing the dose, etc.*"

The Review Report failed to point out any particular problems concerning withdrawal other than the above.

(2) Statements in Japanese Package Insert

Meanwhile, *the Important Precautions on point 8 of the Japanese package insert state the following: "Discontinuation of treatment (particularly sudden discontinuation) or dose reduction may result in*

dizziness, perception disturbances (such as paresthesia, electric shock sensation, and tinnitus), sleep disorders (including nightmares), anxiety, irritability, agitation, queasiness, tremors, confusion, diaphoresis, head ache, diarrhea, and the like. Most symptoms appear within several days of discontinuation, are mild to moderate, and resolve in about 2 weeks, but may be severe in some individuals and may take 2 to 3 months or more to resolve."

The package insert states that "*based on the data thus far available, these symptoms are not believed to be caused by drug dependency.*"

However, they are typical symptoms of withdrawal which occur upon the discontinuation of drugs that can cause dependency.

It is stated that the following measures should be taken: "*Take the following precautions when reducing the dose or discontinuing Paxil. (1) Avoid abruptly discontinuing treatment. When discontinuing treatment, gradually reduce the dose over a period of several weeks or several months while monitoring patient condition. (2) In the event that intolerable symptoms develop after dose reduction or discontinuation of treatment, resume treatment at the dose prior to dose reduction or discontinuation, and try reducing the dose more gradually. (3) Advise patients not to stop taking the medication on their own. As symptoms such as dizziness and perception disorders noted above may occur if the patient forgets to take the medication, patients should be advised to be sure to take their medication as directed.*"

These statements are more detailed than those on withdrawal in the package inserts of other SSRI's (sertraline hydrochloride, fluvoxamine maleate) (package insert for fluvoxamine maleate: "*When discontinuing treatment, take precautions such as gradually lowering the dose, as sudden dose reductions and discontinuation have been reported to result in head ache, queasiness, dizziness, anxiety, insomnia, decreased mental concentration, etc.*"), and suggest that withdrawal may be a particular problem with Paxil.

(3) Reports in the Medical Literature

In a review of SSRI's by Motohashi,⁹ it is pointed out, in the section on SSRI ADR, that "SSRI's are highly safe drugs, but that does not mean there are no adverse drug reactions . The most frequent ones encountered with paroxetine are sedation, agitation, diaphoresis, sexual dysfunction, and withdrawal."

Several overseas references reporting on Paxil withdrawal have also

been published, as mentioned in the Review Report⁷ and in the report by D.Healy and D.Mangin (attachment 1), and by R.Hama (attachment 2).

A study using spontaneously reported data in France included many reports of SSRI withdrawal and found a high risk in particular with venlafaxine (not approved in Japan) and paroxetine (Paxil).¹⁰

It is also pointed out that treatment with Paxil during pregnancy may cause drug withdrawal syndrome in newborns.

(4) Case Reports of Adverse Drug Reactions in Japan

In fact, from the FY 2000 to the FY 2008, the MHLW was notified of 21 ADR case reports involving drug withdrawal syndrome in newborns.
8

4. Measures Needed to Prevent Congenital Anomalies in Newborns

(1) Generally Prohibited Use During Pregnancy

Since it is evident, as noted in 2 above, that there is a higher risk of congenital anomalies, particularly cardiovascular anomalies (primarily ventral and atrial septal defects), in newborns when pregnant women are treated with Paxil, its use in pregnant women should be prohibited as a general rule, and should be limited to when no alternative therapy is available.

In this respect, the FDA pointed out, in December 2005, that analysis of the epidemiological studies noted in section 2(1) above, revealed an increased risk of congenital malformations, particularly cardiac malformations, when paroxetine was used in early pregnancy, and the classification indicating the pharmaceutical risk posed to fetuses by the use of Paxil in pregnant women was changed from category C to D¹¹ (Category D refers to when there is clear evidence indicating risk to fetuses based on post-marketing surveillance or studies on people, but use in pregnant woman may be justified by the therapeutic benefits. In contrast, category C means that animal experiments indicate adverse drug reactions in fetuses, but use in pregnant women may be justified by therapeutic benefits in the absence of well-controlled studies on

pregnancy).

The FDA also asked for this to be stated in the Warnings section of the package insert.

(2) Limited Use in Patients with Child-bearing age

Paxil thus involves a high risk of teratogenicity, but it takes time for women to realize they have become pregnant. By the time that a woman who has been using Paxil prior to pregnancy becomes aware that she has become pregnant, a certain amount of time may already have passed during the early stage of pregnancy which involves a high risk of teratogenicity.

Another difficulty is that, even if treatment is discontinued to minimize the effects on the fetus, the medication cannot be discontinued immediately in view of the symptoms of withdrawal associated with Paxil, as outlined in section 3 above.

Therefore, in order to avoid congenital anomalies in newborns, not only must treatment during pregnancy be limited, but the treatment of patients with child-bearing age must be similarly limited.

(3) Patient Explanation and Consent

As noted above, the use of Paxil in women who are pregnant or child bearing age should be prohibited as a general rule, and should be limited to when no alternative therapy is available, but even when Paxil must be used, accurate information on Paxil dependency and the risk of congenital anomalies in newborns , drug withdrawal syndrome in newborns and their PPHN should be provided, and the informed consent of the patient should be obtained when it is used (a decision issued by the Tokyo High Court on January 27, 2005¹² also points out the importance of informed consent for parents with regard to disease which can occur in children when the parents want to have children).

(4) In order to ensure the effectiveness of the measures in section (1) through (3) above, the following issues, section 5, are needed.

5 The Need to Revise the Package Insert

(1) Statements in US Package Insert

As noted in section 4(1), in response to the FDA, the US package insert for Paxil has now been revised as follows.

Specifically, the Warnings state that: *(i) infants born of women who used paroxetine during the first trimester of pregnancy have an increased risk of cardiovascular anomalies, primarily ventricular septal defects and atrial septal defects; (ii) if a patient becomes pregnant while taking paroxetine, alternative therapy should be considered unless continuing treatment is therapeutically justified; and (iii) when women wish to become pregnant or are in their first trimester of pregnancy, treatment should be started only after alternative treatment has been considered.* Use during pregnancy is classified as category D.¹³

(2) Statements in Japanese Package Insert

In Japan, on the other hand, “*the Important Precautions*” section states (this is section is not for most serious warnings in Japan) that “*as the risk of congenital anomalies is reportedly increased in newborns delivered by women treated with Paxil, pregnant woman or women of child-bearing age should start treatment with Paxil only when the therapeutic benefits outweigh risks (see Use During Pregnancy, Delivery, or Lactation),*” while “*the Use During Pregnancy, Delivery, or Lactation*” section states in brackets that “*in overseas epidemiological studies, there was an increased risk of congenital anomalies, particularly cardiovascular anomalies (such as ventral or atrial septal defects), in newborns delivered by women treated with Paxil in the first trimester of pregnancy,*” and provides the details of the studies. However, nothing is stated in the Warnings section.

Regarding the drug withdrawal syndrome and PPHN of newborns , the section of “*the Use During Pregnancy, Delivery, or Lactation*” states that “*there are reports that such symptoms as respiratory distress, cyanosis, apnea, higher ventilation ,epileptic-like seizure ,trembling, hypotonia, hypertonia ,hyperlflexia, jitteriness, irritability, constant crying, drawsiness, temperature instabilitiy, feeding difficulty, vomiting, and hypoglycemia are developed in newborns delivered by women*

treated with Paxil in the late trimester of pregnancy. These symptoms are observed just after birth or within 24 hrs, and are noted at times as drug withdrawal symptom or apparent death. In overseas epidemiological studies, there are reports of increased risk of PPHN in newborns delivered by women treated with SSRI after 20 th week of gestation.”

However ,nothing is described in “*the Warning*” or “*Important Precautions*” section.

(3) Revision of Statement Details

As noted in section 4(1) and (3), the following are needed to prevent congenital anomalies in newborns ,drug withdrawal syndrome in newborns and PPHN: (i)in view of serious effects on fetus and newborns, the use of Paxil during pregnancy should be prohibited as a general rule, and should be limited to when no alternative therapy is available; (ii) in view of the dependency and symptoms of withdrawal when treatment is discontinued as well as the teratogenicity associated with Paxil, its use should be limited not only in pregnant and potentially pregnant women, but also in patients with child-bearing age and (iii)adequate informed consent should be obtained even when treatment is unavoidable. This should be explicitly stated in the package insert.

(4) Revision of Section

The guidelines for package inserts, which were revised as a result of a review¹⁴ by "study groups on the revision of pharmaceutical package inserts" ("Guidelines on Precautions for Prescription Drugs," Notification No. 607 of the PAB, April 1997¹⁵) in response to the death-incident caused by Sorivudine,¹⁶ require information to be written conspicuously in red in the Warnings section at the beginning of package inserts to draw attention to "cases in which fatal or extremely serious and irreversible adverse drug reactions occur, or cases in which the possibility that adverse drug reactions may lead to extremely serious accidents necessitates particular precaution."

In light of the fact that the severity of the teratogenicity and especially the cardiac malformations caused by Paxil necessitated cardiac surgery in some cases, it is clear that the teratogenic risk of Paxil and measures for avoiding that risk qualify as a case that should be

noted in the Warnings section mandated by the above guidelines.

(5) Conclusion

We therefore request the following to be stated in the Warnings:

- 1) that there is an increased risk of congenital anomalies, particularly cardiovascular malformations (primarily ventricular septal defects and atrial septal defects), drug withdrawal syndrome and PPHN in newborns delivered by women treated with Paxil
- 2) that treatment should be discontinued or replaced with alternative treatment when patients being treated with Paxil become pregnant unless continuing treatment is clearly therapeutically justified;
- 3) that women who are pregnant or child-bearing age should not, as a general rule, take this medication, and should start treatment only after alternative treatment has been considered; and
- 4) that when Paxil must be used, the patient's informed consent should be obtained after a full explanation of the dependency and the risk of congenital anomalies in newborns.

6. Raising Patients' Awareness

Currently, the MHLW recommends that pharmaceutical industries draft Patients' Information Guide (based on the administrative guidelines on "Memorandum on Drafting Patients' Information Guide," and "Operation of Patients' Information Guide").

For Paxil, Patients' Information Guide on aggravation of impulsiveness has been drafted. However, nothing is stated in *the Guide* on congenital anomalies, PPHN and drug withdrawal syndrome in newborns. The GSK should at least provide Patients' Information Guide on the congenital anomalies in newborns.

The present Patients' Information Guide is not intended to answer patients' questions directly, thus the contents are not easy to understand. (Regarding the congenital anomalies in newborns by Paxil, the difference is obvious in comparison with the FDA or the EMEA). In addition, the access to the information is limited to internet.

Therefore, we request that the GSK provide pregnant women as well as patients with child-bearing age with digestible type of information, such as those in "Frequently Asked Questions" format. The GSK should also sufficiently raise patients' awareness by improving contents and methods, such as disseminating Patients' Information Leaflet at

pharmacies.

7. The Need for a Fact-Finding Study

As noted previously, the results of overseas epidemiological studies revealed the risk that fetuses may be affected by treatment during early pregnancy, and Paxil-induced congenital anomalies, especially ventral and atrial septal defects, have been reported in the form of ADR case reports to the MHLW.

However, the package insert fails to provide adequate warnings of that risk, and the risks have not been fully publicized. It is therefore possible that the relationship between Paxil and congenital anomalies, PPHN and withdrawal syndrome occurring in newborns as a result of such adverse drug reactions has been overlooked and unreported, or that the drug is being widely used by pregnant women or women with or child-bearing age.

Fact-finding studies and epidemiological studies on the use of Paxil in pregnant women should therefore be promptly conducted to implement appropriate safety measures, and the establishment of a research group for that purpose is essential.

8. Summary

In view of the above, as noted in the Purpose of the Demand, we request the followings: (a) the package insert be revised; (b) sufficient awareness be raised using Patients' Information Leaflet etc; and (c) a fact-finding study be conducted.

Attachments

- 1 David Healy, Derelie Mangin; Safety of Antidepressants in Pregnancy With Particular Reference to Paroxetine (Paxil) (July 21, 2009)
- 2 Hama R. On Reproductive Toxicity of Paroxetine (Paxil): Toxicities to Fetus and Newborn--Focusing on the Neonatal Withdrawal toxicity and Persistent Pulmonary Hypertension of the Newborn, Web-Kusuri-no-Check No 135 (Oct 21 2009). Digest version will be

published on the October 2009 issue of “The Informed Prescriber”.

-
- ¹ Pharmaceutical Affairs Handbook 2009
 - ² 2 Package Insert for Paxil Tablets 10 mg and Paxil Tablets 20 mg, revised May 2009, (Ver. 16).
 - ³ <http://www.fda.gov/cder/drug/advisory/paroxetine200512.htm>
 - ⁴ GSK Clinical Study Register Study No. WEUSRTP2280; Paroxetine Use in First Trimester of Pregnancy and the Prevalence of Congenital, Specifically Cardiac, Malformations: Systematic Review and Meta-Analysis of Epidemiological Data.
<http://www.gsk-clinicalstudyregister.com/files/pdf/24089.pdf> (accessed 22 July 2009).
 - ⁵ Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, Mitchell AA. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med.* 2006 Feb 9;354(6):579-87.
 - ⁶ GlaxoSmithKline "Data on paroxetine hydrochloride hydrate and Paxil tablets 10 mg and Paxil tablets 20 mg
 - ⁷ Director of National Institute of Health Sciences, "Review Report" (NIHS No. 2706) (July 19, 2007)
 - ⁸ http://www.info.pmda.go.jp/fukusayou/menu_fukusayou_attention.html
 - ⁹ "Nobutaka Motohashi "Therapy: Antidepressant Types, Pharmacological Properties, and Clinical Efficacy – Selective Serotonin Reuptake Inhibitors," (*Japanese Journal of Clinical Medicine*, Vol. 59, No. 8, page 1519) (August 2001)
 - ¹⁰ Trenque T, Piednoir D, Frances C, Millart H, Germain ML. Reports of withdrawal syndrome with the use of SSRIs: a case/non-case study in the French Pharmacovigilance database. *Pharmacoepidemiol Drug Saf.* 2002; 11(4): 281-3.
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108527.htm>
 - ¹¹ Tokyo High Court, Decision Issued January 21, 2005 (Reports of Precedents No. 1953, page 132)
 - ¹² PAXIL PRESCRIBING INFORMATION (©2009, GlaxoSmithKline.)
 - ¹³ 2005 Health Science "Study on Revisions of Pharmaceutical Package Inserts" Report (March 22, 1996)
 - ¹⁴ Notification No. 607 of PAB "Guidelines for Precautions for Prescription Drugs (April 25, 1997)
 - ¹⁵ PAB "Results of Study on Adverse Drug Reactions Caused by Sorivudine," (September 1994)
 - ¹⁶