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Demand for Publication of Information Related to Post-Marketing Clinical Trials on Children and Adolescents Using the Antidepressant Paxil

I. Purpose of the Demand

We are requesting the following information on "Clinical Evaluation of Efficacy and Safety of Paxil Tablets in Children and Adolescents with Major Depressive Disorder: Placebo-Controlled, Double-Blind, Parallel Group Study."

(1) The justification for determining the conduct of this study to be necessary and valid (how and why the conduct of the trial was determined to be necessary and valid)
(2) In particular, if the premise of conducting the clinical study is that effects can be expected for Japanese children, what information was used as justification for making that determination
(3) The most recent version of the study protocol (including records of previous revisions)
(4) Subject recruitment status (the names of the sites participating in the study to date, the number of people recruited at each site, and the Patient Information Sheet used at each site)
(5) Information on adverse events reported to date (information on number of emergent cases and clinical course of individual cases, etc.)

II. Reason for the Demand

1. Introduction

(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 was the top-earning antidepressant in the Japanese market (50 billion yen) in 2007.[1)] The dosage forms in Japan comprise a 10 mg tablet and a 20 mg tablet. It is indicated for "depression, depressed state, panic disorder, and obsessive compulsive disorder," but is not indicated for children. Furthermore, the warnings in the current package insert state: "Carefully review the Indications when using Paxil to treat patients with major depressive order under the age of 18, as it has been reported that efficacy could not be confirmed in overseas placebo-controlled studies on major depressive disorder in 7- to 18-year olds, and it has also been reported that there is an increase in the risk of suicide (see warnings in "Indications," "Careful Administration," "Important Basic Precautions," and "Pediatric Use"). It has been pointed out that efficacy has not been confirmed and that the use of Paxil in children is associated with serious risks.[2)]

(2) Clinical Studies of Depression in Children

According to data published on overseas and Japanese clinical study register websites, a "Clinical Evaluation of Efficacy and Safety of Paxil Tablets in Children and Adolescents with Major Depressive Disorder: Placebo-Controlled, Double-Blind, Parallel Group Study" is currently being conducted.[3,4)]. In the published data, it is stated that the purpose of the study is "to evaluate the efficacy and safety of oral paroxetine 10 to 40 mg/day (initial dose: 10 mg/day) once a day after dinner for 8 weeks in children and adolescents with major depressive disorder." [4)] The subjects are 7 to 17 years of age. As noted above, overseas studies have not confirmed efficacy in patients in this age group, and increases in the risk of suicide have been reported. This same information also indicates that the clinical trial is being conducted only in Japan.[3,4)]

We strongly desire the disclosure of detailed information and a public re-examination of the question of whether it is truly necessary and valid to conduct a new clinical trial with Japanese children on a drug whose efficacy could not be confirmed in overseas clinical trials and which furthermore is suggested to potentially increase the risk of suicide.

2. Risks of Paxil Tablets

(1) Aggression

On May 8, 2009, the MHLW reported the results of a survey on the relationship between SSRI/SNRI medication and harmful acts against others such as injury to the Pharmaceutical Affairs and Food Sanitation Council, Committee on Safety of Drugs.[5)]

This survey was conducted by the Office of Safety in the Pharmaceuticals and Medical Devices Agency to investigate cases of side effects which have been reported since the drug first came out on the market in 1999 (Paxil 2000) until March 2009. The results of the survey revealed that 173 and 65 incidents of adverse events corresponding to "hostility/aggression" were reported with paroxetine hydrochloride and fluvoxamine maleate, respectively. These reports included 26 and 7 "cases of actual harmful acts against others" during treatment with paroxetine hydrochloride and fluvoxamine maleate, respectively, and it was stated that these 26 and 7 cases were closely examined. It was concluded that a causal relation between treatment with these drugs and the harmful acts against others could not be ruled out in 2 of the 26 and 7 incidents. Upon receiving these results, the MHLW ordered the package insert to be revised on May 8, 2009, and the Precautions were supplemented with details such as those calling attention to "Excitement, Irritability, Hostility, and Aggression."

Out of the adverse events qualifying as "hostility/aggression," 45 incidents with paroxetine hydrochloride and 17 incidents with fluvoxamine maleate were reported as "cases that could have led to harmful acts against others," but these were not closely examined. There were 102 and 41 "cases with no harmful acts against others" with paroxetine hydrochloride and fluvoxamine maleate, respectively. Whether or not a patient actually committed a harmful act against another is not the issue, and "cases that could have led to harmful acts against others" should at least be closely examined just as the "cases of actual harmful acts against others" were. Measures which should be taken in view of the above must be re-examined.

(2) Risk of Increased Suicide-Related Events in Children

In October of 2002, the BBC television special "Panorama" caused quite a stir in taking up the issue of adverse events such as "attempted suicide" associated with paroxetine hydrochloride. The Dept. of Health in Great Britain was subsequently advised on June 10, 2003 by CSM (Committee on Safety of Medicines) that "paroxetine hydrochloride should not be used in children and adolescents under the age of 18 years as its efficacy has not been demonstrated and there are greater risks," and its use was contraindicated in children and adolescents under the age of 18 years. Following the UK, the FDA in

the United States also issued an advisory on June 19, 2003 not to use paroxetine hydrochloride to treat major depressive disorder in children and adolescents under the age of 18 years.
In step with the responses of the regulatory authorities in Europe and the US, the use of paroxetine hydrochloride was contraindicated in patients with major depressive disorder under the age of 18 in Japan as well.

Subsequent review by regulatory authorities in Europe and the US of the results of clinical study results on all antidepressants in addition to paroxetine hydrochloride revealed an increased risk of "suicidal ideation and attempted suicide with all antidepressants," but on the grounds that many patients, on the other hand, have benefited from treatment with antidepressants," it was determined that the use of antidepressants would no longer be contraindicated in pediatric patients in the US, and the ban was also lifted in April of 2005 in the UK. In response to this development, the "Contraindications" were deleted in the revised Japanese paroxetine hydrochloride package insert in January 2006. The four following reasons were given to justify the revision at that time.[6)]

① The lack of post-marketing reports of suicide-related side effects in Japan in patients under the age of 18 years

② The availability of case reports suggesting the usefulness of the drug in patients with major depressive disorder under the age of 18

③ The insistence of the Japanese Society for Child and Adolescent Psychiatry that this treatment was a necessary option

④ The absence of such contraindications in the US and Europe at present

As of May 2009, the PMDA reported at least 5 incidents of completed suicide, attempted suicide, or suicidal ideation in cases between the ages of 10 and 19 as adverse events of paroxetine hydrochloride in "Information on Case Reports of Suspected Side Effects." That is to say, ① above no longer applies.

In addition, it was reported in "SSRI for depression in children and adolescents" in the Cochrane Systematic Review (March 2007, revised) that combined analysis of three randomized comparative studies conducted in Europe and the US revealed that suicide-related events occurred 2.43 times more in treatment with paroxetine hydrochloride compared to placebo (however, the 95% confidence interval was 1.00 to 5.87 in use for major depressive disorder, which is fairly significant). Similar results were also confirmed in the meta-analysis by Bridge et al published in April 2007.[8)]

(3) Safety Problems in Japanese Individuals (potential for higher concentration in blood due to metabolic enzyme deficiency)

Paroxetine hydrochloride is metabolized primarily through the action of a metabolic enzyme in the liver referred to as CYP2D6. It has been pointed out that the pharmacokinetics of paroxetine hydrochloride metabolism are nonlinear, where doubling the dose results in more than double an increase in blood concentration (for example, assuming that a 20 mg dose results in a certain blood concentration, doubling the dose to 40 mg results in a blood concentration 2.48 times greater).[2)] This is thought to occur because the action of the CYP2D6 metabolic enzyme becomes saturated at or over a certain dose. Because such metabolic enzyme action also varies from individual to individual, there is concern that the concentration of paroxetine hydrochloride in blood may increase rapidly depending on the dose and depending on the individual.

It has furthermore been pointed out that there is a risk that drugs (such as paroxetine hydrochloride) may not be metabolized and that the concentration in blood may increase because the metabolic enzyme activity is lower in some genotypic variants of CYP2D6 polymorphisms. So far, this type of genotypic variant of CYP2D6 is extremely rare in Japanese individuals (less than 1%), but it was recently found that a specific variant known as CYP2D6*10 occurs in about 39% of the Japanese population. It turns out that paroxetine hydrochloride is not metabolized by individuals with this variant, and there is concern over the risk of increased concentrations in blood.

(3) Efficacy of Paxil Tablets

－Efficacy for Major Depressive Disorder in Children Not Shown in Overseas Clinical Studies or Meta-Analysis－

The results of clinical studies in children and adolescents have been published in "Paroxetine and pediatric and adolescent patients" on the GlaxoSmithKline website. The efficacy of paroxetine hydrochloride compared to placebo was not confirmed in any of Studies 329, 377, or 701 in patients with major depressive disorder.[9)-11)] ※

For example, Table 1 summarizes the results for the efficacy of paroxetine hydrochloride in adolescents in these three studies. In the results for all the studies, no statistically significant differences in the proportion of individuals who were rated effective were found between the paroxetine hydrochloride group and the placebo group.

※ In October 2004, we submitted a demand seeking the publication of data and the like on clinical trials on SSRI, including paroxetine hydrochloride (http://www.yakugai.gr.jp/topics/file/041027ssriyouboushо.pdf).

Table 1: Efficacy of paroxetine hydrochloride (from randomized studies)

Study ID	Percentage rated effective (%)		Statistical test (P value)
	Paroxetine hydrochloride group	Placebo group	
Study 329 [9]-	67(60/90)	55(48/87)	0.1
Study 377 [10]	60(107/177)	58(53/91)	0.7
Study 701 [11]	52(27/52)	45(24/53)	0.5

The results of the three studies in Table 1 were also collectively analyzed by meta-analysis in the above-mentioned "SSRI for depression in children and adolescents" in the Cochrane Systematic Review (March 2007, revised). The combined results confirmed not only an increase in suicide-related events but also virtually no difference in effects between paroxetine hydrochloride and placebo (in terms of therapeutic efficacy for major depressive disorder, assuming a therapeutic response rate of 1 in treatment with placebo, the rate for paroxetine hydrochloride was 1.09; 95% confidence interval: 0.95 to 1.26).[7] Thus, the fact that not only the individual comparative clinical studies failed to demonstrate efficacy superior to placebo, but that they collectively revealed no efficacy in meta-analysis (a method with greater statistical power) can be considered far more reliable evidence than case reports of effectiveness based on clinical experience with the use of the drug.

And now that findings based on overseas clinical study results have thus been collected, the necessity and validity of conducting a new clinical trial for the purpose of obtaining data in Japanese children can be guaranteed? If this can be guaranteed, the businesses responsible for conducting the clinical trial and the regulatory agencies need to show the reasons.

4. Validity of Conducting the Clinical Trial

(1) Problems with Diagnosis of Depression in Children

The proper conduct of a clinical study presupposes the ability to appropriately select patients with the disease under study based on appropriate diagnostic criteria, but doubts have been raised as to whether the very concept of the disease of depression in children has been established in the first place.[12] According to information on the clinical study register website, the diagnostic criteria for "major depressive disorder (MDD) in children and adolescents" which is being studied in the titled clinical trial are supposed to be based on DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision, by the American Psychiatric Association), but this manner of working

diagnostic criteria (where the presence of absence of disease is determined based on a combination of symptoms, not on the basis of any cause of disease) are inherently limited, and it is difficult to diagnose psychiatric diseases in children. Furthermore, no consensus has necessarily been achieved among psychiatrists about the treatment of depression in children, such as whether drug therapy should be carried out or whether priority should be given to psychotherapy.

In view of this state of affairs, it turns out that childhood depression is a disease for which no appropriate diagnosis has yet been established, the selection of patients with the disease under study based on appropriate clinical criteria therefore cannot be guaranteed, and no proper clinical trial can be conducted. In other words, this means that the conduct itself of the study will not be valid.

(2) Ethical Problems in the Conduct of Clinical Trials in Children

According to current ethical guidelines on clinical studies, "informed consent can be obtained from a legal representative when the subject is a minor (unmarried individuals under the age of 20 years). However, even in these cases, researchers must make every effort to give a full and complete explanation in easy-to-understand language to ensure the subject has a thorough understanding. In addition, when the subject is a minor of 16 years or older, informed consent must be obtained from the subject as well as the legal representative."[13] The GCP "Guidance on Clinical Trials of Pharmaceutical Products in Children" also states that "As a rule, legally defined informed consent cannot be obtained from patients who are children. The parents or a legal guardian are therefore presumed to be responsible for a subject's participation in a clinical trial. Informed consent should be obtained from a legal guardian in accordance with local laws and regulations. All subjects should be given as full and complete an explanation as possible about the clinical trial in words and language they can understand. When appropriate, assent (consent from juvenile subjects not subject to statutory regulation) may be obtained from subjects for participation in a clinical trial." [14]

As has already been pointed out, this study is a clinical trial on a drug for which efficacy has not been demonstrated in overseas clinical trials, and is a study in which the subjects will be at risk for attempted suicide or aggression-based harmful acts against others. It is argued that clinical trials are needed in Japan in order to develop new drugs or to expand indications for children in view of the current state of affairs in which virtually no psychotropics are covered by insurance yet most are employed in off-label use in the psychiatric treatment of children and adolescents, but this study is a clinical study on a drug for which efficacy has been ruled out and risks have been pointed out in overseas trials, and we therefore believe the validity of conducting the trial is strongly negated.

When children are the subjects of clinical trails, ethical considerations and safety assurance must be guaranteed on behalf of the subjects even more than for adults. To that end, it should be

assumed that the efficacy and safety of the study drug have first been confirmed at least in adults. Although paroxetine hydrochloride has been shown to be effective to a certain extent for depression in adults, it must be concluded that this study has very little validity, considering that not only have the risks of aggression and harmful acts against others been pointed out, as noted above, but that the efficacy in children has not been demonstrated, and treatment is accompanied by the risk of suicide.

If the primary claim regarding the validity of conducting the study is that the data on the efficacy and safety of paroxetine hydrochloride for major depressive disorder obtained in this study will, as a result, bring about benefits for children and adolescents with depression, and that these benefits will outweigh potential disadvantages to participants in the study, this must be fully explained to the subjects so that they understand. However, the subjects in this study are 7 to 17 year old children and adolescents. According to the Protocol Summary for 112487 (clinical study register information) published by GlaxoSmithKline on the Clinical Study Register, subjects can participate in the study with the informed consent of a legal representative (which mostly applies to parents). The informed consent of the individuals themselves who are 12 years of age or older is also preferred, and efforts will also be made to obtain informed consent from the individuals themselves who are under the age of 12 years.[15)] As already noted above, there are problems in terms of efficacy and safety in this study, and there are serious doubts about whether or not parents and pediatric or adolescents patients can make an informed decision to participate in the study based upon a thorough understanding, particularly children and adolescents, even after a full and complete explanation. The possibility of consent being given to participate in the study despite an imperfect understanding also cannot be ruled out, and there is grave concern that the participation of children and adolescents may incur detrimental risks.

5. Conclusion

In view of the above, the necessity and validity of conducting this trial should be re-examined on the basis of a full disclosure of detailed information. We also seek the full disclosure of all future clinical and research information submissions regarding details that have already been implemented and data that has been obtained. The conduct of this study was also addressed by the Pharmaceutical Affairs and Food Sanitation Council, First Committee on New Drugs on August 24, 2006. The MHLW should express an opinion on (1) the justification for determining the conduct of this study to be necessary and valid, and (2) the justification for determining that effects are expected for Japanese children as the premise for conducting the clinical study, as indicated in the Purpose of the Demand noted above.

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