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Mr. Yoichi Masuzoe, Minister of Health, Labour, and Welfare

Mr. Kazuhiko Mori, Director, Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

Mr. Hiromitsu Iwasaki, President and Chief Executive Officer, Pfizer Japan Inc.

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 for Safety Measures for Smoking Cessation Aid "Champix"

I. Purpose of the Demand

We request the following.

1. Revise the package insert as follows.

(1) State in the "Warnings" that adverse events such as depressed mood, anxiety, irritability, agitation, changes in behavior, suicidal ideation, and suicide have been reported.

(2) Clearly state that these symptoms have been reported in patients who continued to smoke while using Champix, and revise the inappropriate statements in the current package insert which give the impression that such symptoms were caused by smoking.

(3) State that patients should be advised to avoid driving, operating machinery, or performing other hazardous activities.

(4) Limit indications for Champix to when nicotine replacement therapy cannot be used.

2. Step up efforts to reduce risk based on the action taken by the FDA in the United States.

3. Promptly conduct a pharmacoepidemiological study with a design that includes an appropriate comparison group to clarify the relationship with severe neuropsychiatric disorders before and after treatment with Champix.

II. Reason for the Demand

1 Summary of Champix and Occurrence of Major Adverse Events

(1) Summary of Champix

The smoking cessation aid "Champix" (generic name: varenicline hydrochloride) by Pfizer Japan Inc. is indicated as "an aid to smoking cessation in nicotine-dependent smokers." It received marketing authorization in January 2008 and was added to the NHI price list (with some restrictions) in April, and the product was launched in May.

Champix is a product for which "early post-marketing phase vigilance" was specified.

Conventional smoking cessation aids are nicotine replacement therapy drugs. Nicotine patches are used as the standard dose form, but nicotine gum is also available. In contrast, "Champix" is an oral medication that is an α4β2 nicotine receptor partial agonist, with a novel mechanism of action.

In the United States, it was launched under the brand name of Chantix by Pfizer in May 2006. In Japan, marketing authorization was obtained through clinical development involving bridging studies using data from Europe and the United States.

(2) Adverse Events Involving Neuropsychiatric Disorders

Adverse events involving neuropsychiatric disorders such as affective disorders and aggression were already mentioned in the package insert when the drug was launched in the United States in May 2006, but it was not until around the summer of 2007 after the drug came out on the market that people became aware of these adverse events. When replying to a question by a user on the Internet, Dr. Antonio Howell commented on the abundant references to neuropsychiatric disorders which he had noticed in the package insert, and he was approached by patients and families who had seen the exchange. In another incident in September 2007, the musician, Carl Albrecht, was shot to death by a neighbor who was frightened of Albrecht's abnormal behavior 1 week after starting the medication, and the adverse events of varenicline became a sudden focus of attention [1]。

From May 2006 to December 2007, the FDA received reports of 227 incidents of suicidal behavior or suicidal ideation, 397 incidents of possible psychosis, and 525 incidents of aggression in the US [2].

Pfizer revised the package insert in January 2008, and added a new "Neuropsychiatric Symptoms" section to the Warnings to draw attention to adverse events (adverse reactions) such as behavioral abnormalities, agitation, depression, suicidal ideation, and suicidal behavior.

According to Pfizer Japan's "Champix Application Data Summary" published after marketing authorization in Japan, the incidence of psychiatric disorders which led to discontinuation of treatment was 2.4% (3 out of 126 patients) in the placebo group but was 3.6 times higher at 8.0% (20 out of 251 patients) in the varenicline group in a randomized comparative trial on the continuous use of varenicline for one year in Europe and the US. These were reported to include insomnia (8 patients in the varenicline group vs. 1 patient in the placebo group), abnormal dreams (6 patients vs. 0 patients), depression (5 patients vs. 1 patient), and emotional excitement (3 patients vs. 0 patients). Nervous system disorders also showed up in 9 patients vs. 1 patient [4].

In a total of four Phase III randomized comparative studies conducted in Europe and the US, there was a total of five reports, comprising one death by suicide and one serious event each of suicidal ideation, psychotic disorder, acute psychosis, and grand mal convulsion. However, there was only a single incident of schizophrenia with placebo [5].

In Japan, as well, as of December 31, 2008 post-marketing, 25 incidents of psychiatric disorders such as suicidal ideation, completed suicide, and abnormal behavior, and 18 incidents of nervous system disorders such as loss of consciousness, decreased consciousness, and stupor had been reported as "cases of adverse reactions suspected of being caused by Champix" by medical institutions, pharmacies, and pharmaceutical companies [6].

In addition, based on the results of "early post-marketing phase vigilance" from May 8 to November 7, 2008 (1857 hospitals and 8903 clinics), it was reported that there were 1536 incidents of adverse events (adverse reactions) in 985 cases, among which 425 incidents of neuropsychiatric disorders in 330 cases were the most frequently reported after gastrointestinal disorders. Symptoms lasted 2 or more weeks in 84 incidents in 204 cases (41%) in which it was possible to confirm the time it took for symptoms of neuropsychiatric disorders that had developed to resolve. 61 serious incidents in 36 cases were reported, but two thirds comprised 38 incidents in 23 cases of neuropsychiatric disorders, such as 3 incidents of depression with suicidal depression, 2 incidents of suicidal ideation, 1 incident of completed suicide, 2 incidents of abnormal behavior, 1 incident of violence-related symptoms, 2 incidents of psychiatric disorders, 2 incidents of loss of consciousness, and 1 incident of altered state of consciousness [7].

"Champix" is a nicotine receptor partial agonist, but nicotine receptors are not simple, and there are many types, each of which has pharmacological action, stimulates the release of many neurotransmitters such as dopamine, and affects neuropsychiatric function in a variety of ways [8][9]. The adverse events involving psychiatric disorders associated with Champix may be causally related in view of the pharmacological action of the drug, which is a nicotine receptor partial agonist and also a receptor antagonist.

(3) Reported Adverse Events and Usefulness of Champix

The fact that the abstinence rate in clinical studies of Champix was in the 20's to 40's indicates that it is difficult to quit smoking even when taking Champix. In the meanwhile, there have been reports of major adverse events, as noted above.

It is often possible to quit smoking without dependence on medication anyway, as is evident in the successful smoking cessation rate of 20% or more shown in placebo groups in comparative clinical studies of Champix or nicotine patches in Japan [10].

Regarding Champix, Pfizer Japan Inc. has commented that "the risks associated with the administration of varenicline as a smoking cessation aid for nicotine-dependent smokers must be minimized" [11], but the serious adverse events that have been reported ultimately detract from the efficacy of Champix.

Nicotine agents (nicotine replacement therapy agents) are the standard alternative to Champix. As noted above, drug therapies do not play a major role in overcoming nicotine dependency, but when drug therapy is considered, nicotine agents are the drug of first choice. Given the risk of serious adverse reactions, the use of Champix should be limited to when nicotine agents cannot be used.

In this regard, in assessing the medical costs of nicotine dependency covered by insurance, the covered costs of Champix can be assessed only when prescribed. A condition is that the medical coverage for nicotine dependency cannot be assessed again until after one year from the date of the first assessment. In cases where the use of Champix is limited to when nicotine agents cannot be used, this stipulation can become an impediment, and the impediment must be eliminated.

2. Differences in the Japanese Package Insert

(1) US Package Insert

The US package insert (revised May 2008) states the following (bold text same as in original) [12].

<Note: On July 1, 2009, the FDA asked Pfizer to further state this in the Boxed Warnings [19]>

[Warning: Neuropsychiatric Symptoms]

Serious neuropsychiatric symptoms have occurred in patients being treated with Chantix. Some cases may have been complicated by symptoms of nicotine withdrawal in patients who stopped smoking. However, some of these symptoms have occurred in patients who continued to smoke. All patients being treated with Chantix should be observed for neuropsychiatric symptoms including changes in behavior, anxiety, depressed mood, suicidal ideation, and suicidal behavior. These symptoms and worsening of pre-existing psychiatric illness have been reported through post-marketing surveillance in some patients who used Chantix in an attempt to quit smoking. Patients with serious psychiatric illness such as schizophrenia, manic depression, and clinical depression did not participate in pre-marketing clinical studies of Chantix, and the safety and efficacy of Chantix in these patients have not been established.

Advise patients and caregivers that patients should stop taking Chantix and should immediately contact a medical institution if anxiety, depressed mood, or changes in behavior that are out of the ordinary in the patient are observed, or if suicidal behavior appears.

(2) Japanese Package Insert

Meanwhile, the Japanese package insert (revised May 2009) states the following [13].

[Precautions: 2. Important Precautions]

(2) It has been reported that attempts to quit smoking, with and without treatment, are associated with a variety of symptoms (such as discomfort, depressed mood, insomnia, irritability, frustration, anger, anxiety, attention concentration difficulties, restlessness, decreased heart rate, increased appetite, and weight gain). Underlying psychiatric illness may worsen. Although the causal relation is not clear, there have also been reports of depressed mood, anxiety, irritation, agitation, changes in behavior, suicidal ideation, and suicides when Champix has been used in an attempt to quit smoking, and patients should therefore be carefully monitored during treatment with Champix. Patients should also be advised to stop taking Champix and to immediately contact a physician or the like if these symptoms or behaviors occur.

The statements in the Japanese package insert are extremely ambiguous and inadequate.

First of all, these statements appear in the "2. Important Precautions" section of the "Precautions" in the Japanese package insert, but they should appear in the "Warnings" because they correspond to "cases in which an adverse reaction may develop, leading to extremely serious accidents,

particularly when an alert needs to be issued," which was established as a condition for Warnings in descriptions of ethical drugs (Notification No. 607 issued in 1997).

In addition, the Japanese package insert comments at great length only that quitting smoking may cause neuropsychiatric symptoms, and fails to clearly state that neuropsychiatric symptoms have also been reported in patients who continued to smoke while using the drug, as stated in the US package insert by Pfizer. The double standard occasioned by the significant differences between Japan and the US despite the fact that both are package inserts by the same company, Pfizer, must be remedied promptly.

3. Differences in Safety Measures Between Japan and the US

(1) Responses by the FDA in the US and the ISMP (Institute for Safe Medical Practices)

In view of the conspicuously large number of reports of varenicline in the voluntary Adverse Event Reporting System (AERS), the FDA issued a safety alert in November 2007 that the safety of Chantix was being reviewed (review focused on adverse events) [14].

In February 2008, the FDA issued a "Public Health Advisory: Important Information on Chantix" to alert healthcare professionals, patients, and the public to Chantix [15]. It was stated that the company had been asked to revise the package insert because of the strong possibility that the adverse events were caused by varenicline, and it also stated that a Medication Guide was being prepared with the company to fully alert patients through pharmacies. In May 2008, the FDA revised the Public Advisory to show that the package insert had been revised and that the Medication guide [16] had been finalized, and prepared a further safety alert [17]. On January 15, 2009, Chantix was addressed in the FDA Drug Safety Newsletter [18].

On July 1, 2009, based on the authority to ensure safety in the FDA Revitalization Act, Pfizer was ordered to note the risks of neuropsychiatric disorders in the Boxed Warnings, which constitute the most serious warnings in package inserts [19].

The FDA thus bolstered warnings, attempted to reduce risks, and advanced safety through these various steps.

In May 2008, the ISMP analyzed the varenicline adverse events reported to the FDA, and warned of the risk of a wide range of other adverse reactions in addition to neuropsychiatric disorders. Among these were 173 incidents of adverse events leading to accidents which were reported between

May 2006 and December 2007, including 28 incidents of traffic accidents, and the FDA was thus requested to issue a strong warning to avoid handling machinery while using Chantix [2].

(2) Delay in Japanese Response

Champix received marketing authorization in January 2008 in Japan. During the review stage, it was reported that adverse events such as neuropsychiatric disorders had become a problem in the US, and that safety alerts had been issued. The MHLW nevertheless approved Champix unconditionally, and took no subsequent action such as that taken in the US. Greater efforts should be promptly taken to reduce risks.

4. Conduct of Pharmacoepidemiological Study

Healthcare professionals and patients should be fully and appropriately alerted even before the causal relationship between the smoking cessation aid "Champix" and any adverse events is determined.

There is an urgent need to simultaneously conduct a pharmacoepidemiological/analytical epidemiological study to clarify the causal relationship between "Champix" and adverse events such as neuropsychiatric disorders. This study must learn from the example of the influenza therapeutic Tamiflu, must be focused on the relationship between "Champix" and adverse events such as neuropsychiatric disorders, and must be conducted with a design that includes appropriate comparison groups to clarify the relationship to adverse events before and after treatment with the drug.

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