Appendix 6.
Japanese Dear Doctor Letter

ZY 4051 1633

IMPORTANT

April 2002
No. 02-1

Emergency Safety Information

Regarding diabetic ketoacidosis and diabetic coma due to increased blood glucose during administration of an antipsychotic agent, Zyprexa® Tablets (Olanzapine)

Since the marketing of this product in June 2001, 9 serious cases (including 2 cases of death) with hyperglycemia, diabetic ketoacidosis, and diabetic coma have been reported for which causal relationship with this product cannot be denied (estimated number of patients treated with this product: about 137,000, as of the end of December 2001). (Possible development of) hyperglycemia has been included in "Precautions" to raise awareness. However, as the result of the assessment of these serious cases, the "Precautions" section has been revised and "Contraindications" and "Warnings" have been added. For use of this product, special cautions should be taken regarding the following matters. In the event of hyperglycemia, please contact the medical representatives of Eli Lilly Japan K.K.

1. Do not administer to patients with diabetes mellitus and those who have a history of diabetes mellitus.

In patients with diabetes mellitus and those who have a history of diabetes mellitus, blood glucose may increase and metabolic status may be deteriorated acutely, thus do not administer this product to these patients.

2. During administration of this product, observe sufficiently with such as measurement of blood glucose.

With the administration of this product, from marked increase in blood glucose, serious adverse reactions such as diabetic ketoacidosis, diabeteic coma etc. may appear leading potentially to death. Thus, observe sufficiently with such as measurement of blood glucose during administration of this product.

3. Explain sufficiently to the patient and family members.

Upon administration of this product, explain sufficiently to the patient and family members possible occurrence of serious adverse reactions, such as diabetic ketoacidosis and diabetic coma etc. Provide guidance to them to see a physician suspending administration if such symptoms as thirst, polydipsia, polyurea or frequent urination etc. appear.

We also report the revisions made to the "Warnings," "Contraindications" and "Precautions" as shown on the back of this overleaf.

Where to contact: Medical Information Services, Eli Lilly Japan K.K.
7-1-5 Isogamidoori, Chuo-ku, Kobe 651-0086
Tel: 0120-360-605 Fax :078-242-9299

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<Case Presentation>

<table>
<tr><th>No.</th><th>Sex, age, reason for use (complications)</th><th>Clinical course and treatment</th></tr>
<tr><td>1</td><td>Male, in 20's
Schizophrenia
(Hyperlipidemia, hepatic disorder)</td><td>
Diabetic coma
The patient was diagnosed as having schizophrenia about 10 years ago. He was obese with 170 cm in height and 90 kg in body weight. Came to the hospital about 2 years ago, and had a tendency for weight gain and overeating. Receiving diet therapy for pre-existing hyperlipidemia.
About 3 months before administration: Treated with fenofibrate. Triglyceride decreased temporarily.
About 2 months before administration: Switched to quetiapine fumarate. Triglyceride increased again.
Administration initiation day: Initiated treatment with olanzapine at a daily dose of 10 mg. The body weight was more than 100 kg, and the blood glucose was normal.
Day 15 of treatment: Casual blood glucose was 230 mg/dL. Triglyceride increased to 555 mg/dL. Diabetes mellitus was suspected. The dose of olanzapine increased to 15 mg.
Day 29 of treatment: Further increased appetite. The patient and his family were instructed to follow strictly the diet therapy and life style modification.
Day 43 of treatment: Weight loss of 6 kg in 2 weeks. The patient insisted that he had been on a diet. No particular complaint other than thirst and consumption of a large quantity of juice. The blood tests revealed blood glucose of 723 mg/dL, HbA1c of 10%, triglyceride of 960 mg/dL, total cholesterol of 362 mg/dL, urine glucose of 1 g/dL, and urine ketone body of (+++).
Day 45 of treatment: Brought into a critical care center of another hospital due to cardiopulmonary arrest. At the 2nd cardiopulmonary resuscitation, the spontaneous heart beat was resumed. The blood glucose level was 854 mg/dL. Following resuscitation, treatment for encephalopathy and hyperglycemia was started. CT revealed prominent cerebral edema.
Day 48 of treatment: The patient died.
<table>
<tr><th></th><th>About 3 months before administration</th><th>Day 15 of treatment</th><th>Day 43 of treatment</th><th>Day 45 of treatment</th></tr>
<tr><td>Casual blood glucose (mg/dL)</td><td>137</td><td>230</td><td>723</td><td>854</td></tr>
<tr><td>HbA1c (%)</td><td></td><td></td><td>10.0</td><td></td></tr>
<tr><td>Urine glucose (g/dL)</td><td>Negative</td><td></td><td>1</td><td></td></tr>
</table>
</td></tr>
<tr><td colspan="3">Concomitant medications: timiperone, biperiden hydrochloride, cloxazolam, quetiapine fumarate, fenofibrate, haloperidol, and bromperidol.</td></tr>
</table>

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No.	Sex, age, reason for use (complications)	Clinical course and treatment
2	Male, in 30's Schizophrenia (No complication)	**Diabetic coma** About 8 months before administration: Inpatient treatment started. At the admission, the patient was 170 cm in height and 83 kg in body weight, with the fasting blood glucose of 80 mg/dL. About 4 months before administration: Body weight was 88.5 kg. Tendency for overeating, weight gain, and consumption of a large quantity of soft-drings. About 3 months before administration: After hospital discharge, the patient was followed as an outpatient. Administration initiation day: Initiated treatment with olanzapine at a daily dose of 10 mg. Day 15 of treatment: The patient had thirst, but treatment was continued. The amount of drinking was 2 L per day. Day 17 of treatment: Because of a feeling of swollen throat, visited the otolaryngology department of a general hospital. White spots in oral mucosa and swollen tonsils on both sides were noted and the patient was diagnosed as having acute tonsillitis. Piperacillin 4 g and 500 mL of glucose added solution were administered. Day 18 of treatment: The patient, showing no sign of improvement, was hospitalized into the otolaryngology department of the general hospital. The body weight was 96 kg. Piperacillin 4 g, 1000 mL of glucose added solution, and hydrocortisone 300 mg were administered. The patient had consumed 10 cans of juice on the day. Day 19 of treatment: The patient was found to be in disturbed consciousness, incontinence, and sursumversion on his feet. With the blood glucose of 1655 mg/dL and blood osmotic pressure of 405, a diagnosis of hyperosmolar diabetic coma was given. Treatment was initiated with physiological saline and insulin. About 7 hr after discovery, the blood glucose improved to 980 mg/dL, and the patient regained consciousness. About 10 hr after discovery, the patient developed convulsive seizure and impaired consciousness, and was transferred to ICU. At the admission to ICU, the patient had the blood glucose of 901 mg/dL, HbA1c of 13.6%, hypernatremia, hypokalemia, elevated creatinine, and metabolic acidosis. Thereafter, the systemic conditions of the patient was exacerbated (progress of renal failure), followed by death.
	Concomitant medications: risperidone, lormetazepam, mianserin hydrochloride, rilmazafone hydrochloride, levomepromazine maleate, flunitrazepam, zotepine, biperiden hydrochloride, and triazolam.	

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No.	Sex, age, reason for use (complications)	Clinical course and treatment
3	Male, in 30's Schizophrenia [Psychosis due to central nervous system stimulant, bilateral blepharospasm (tardive dyskinesia), and gout]	**Non-insulin dependent diabetic mellitus, weight gain** Family history of diabetic mellitus (parents) 160 cm in height and 80 kg in body weight. About 6 months before administration: Casual blood glucose was 92 mg/dL. Administration initiation day: Initiated treatment with olanzapine at a daily dose of 20 mg. No other symptoms than the primary disease and the complications. Day 22 of treatment: Lassitude and numbness of feet were developed and worsened. Day 37 of treatment: The patient visited another hospital, and hyperglycemia (casual blood glucose: 298 mg/dL) and HbA1c of 7.0% were detected. Increased appetite and weight gain were observed. The body weight was 95 kg. Day 39 of treatment: The patient came to this hospital, and the olanzapine treatment was discontinued. 7 days after discontinuation: Admitted to another hospital. Casual blood glucose was 162 mg/dL, and HbA1c was 7.0%. 12 days after discontinuation: Hospital discharge. 14 days after discontinuation: An improvement in diabetic mellitus and weight gain. The body weight was 89 kg.
	Concomitant medications: risperidone, nitrazepam, sodium valproate, and allopurinol.	

No.	Sex, age, reason for use (complications)	Clinical course and treatment
4	Female, in 40's Schizophrenia (No complication)	**Hyperglycemia** Unknown history of diabetic mellitus. No familiy history. Prior acute pancreatitis. The patient was 157 cm in height and 66 kg in body weight. 4 months before administration: Although abnormal fasting blood glucose (126 mg/dL) was detected, no close examination such as glucose tolerance test was performed. Therfore, the presence/absence of glucose tolerance abnormality was unknown. Administration initiation day: Initiated treatment with olanzapine at a daily dose of 10 mg. A tendency for polydipsia. Coadministered with haloperidol. Day 50 of treatment: Hyperglycemia (postprandial blood glucose: 521 mg/dL) was detected. The body weight was 67.5 kg. Day 59 of treatment: Olanzapine was switched to risperidone. The blood glucose was 241 mg/dL. The patient was instructed to reduce the consumption of meals and not to eat between meals. 11 days after discontinuation: Fasting blood glucose was 302 mg/dL, and HbA1c was 10.1%. Glibenclamide and voglibose were administered. 17 days after discontinuation: Postprandial blood glucose was 311 mg/dL. 18 days after discontinuation: Fasting blood glucose was 226 mg/dL, and HbA1c was 9.6%. Urine glucose was (+++). The dose of glibenclamide was increased. 25 days after discontinuation: Fasting blood glucose was 214 mg/dL.
	Concomitant medications: brotizolam, sennoside, trihexyphenidyl hydrochloride, and haloperidol.	

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IMPORTANT

Emergency Safety Information

"WARNINGS" , "CONTRAINDICATIONS"and "PRECAUTIONS"

The revisions made to the "Warnings," "Contraindications" and "Precautions" are as shown below. These revisions are made based on the post marketing case reports of hyperglycemia.

【WARNINGS】

1. From marked increase in blood glucose, serious adverse reactions such as diabetic ketoacidosis, diabetic coma etc. may appear leading potentially to death. Observe sufficiently with such as measurement of blood glucose during the olanzapine administration.
2. Upon administration, explain sufficiently in advance to the patient and family members possible occurrence of above adverse reactions. Provide guidance to them to pay attention to such abnormalities as thirst, polydipsia, polyurea, frequent urination, etc., and to see a physician suspending administration immediately if such symptoms appear. See the section on "Important

【CONTRAINDICATIONS(Do not administer to following patients.)】

5. Patients with diabetes mellitus and those who have a history of diabetes mellitus

【PRECAUTIONS】

1. **Careful Administration (Administer with caution to following patients.)**

(6) Patients with risk factors for diabetes mellitus such as family history of diabetes mellitus, hyperglycemia, obesity, etc. (See the section on "Important Precautions").

2. **Important Precautions**

(1) By administration of this drug, marked increase in blood glucose may appear leading to fatal clinical course such as diabetic ketoacidosis, diabetic coma, etc. Observe sufficiently with such as measurement of blood glucose, (appearance of) thirst, polydipsia, polyurea, and frequent urination during the olanzapine administration. In particular, patients with risk factors for diabetes mellitus such as hyperglycemia, obesity, etc., blood glucose may increase, leading to acute worsening of metabolic state.

(2) Upon administration, explain sufficiently in advance to patients and family members possible occurrence of above adverse reactions. Provide guidance to them to pay attention to such abnormalities as thirst, polydipsia, polyurea, frequent urination, etc., and to see a physician suspending administration immediately, if such symptoms appear,.

(3) As olanzapine may increase body weight, pay attention to obesity, and take appropriate measures such as the diet therapy and exercise therapy, etc. if any sign of obesity is noted.

4. **Adverse Reactions**

(1) **Clinically significant adverse reactions**

1) Hyperglycemia, Diabetic ketoacidosis, Diabetic coma: Hyperglycemia may develop leading to fatal clinical course, such as diabetic ketoacidosis and diabetic coma leading to death. Thus, make a close observation, with such as blood glucose measurement, (appearance of) thirst, polydipsia, polyurea and frequent urination. If any abnormalities are noted, discontinue administration and take an appropriate measure(s) such as administration of insulin.

(Shown revised part only.)

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