Level -1-2

Body weight gain was observed in about 20% of the patients and similar results were obtained in the overseas clinical studies. If the patient who shows weight gain has a risk factor of diabetes mellitus, Olanzapine may induce the onset of DM. Comment on whether or not it is necessary to include this risk in the "Precautions for Use". Also explain the measures taken in this regard in the post-marketing survey.
If recent literature, etc. are available other than the data already submitted on the mechanism of the onset of hyperglycemia by this drug and the relation of hyperglycemia to obesity, submit them.

Response

1) Precautions

It has been pointed out that body weight increase generally occurs with antipsychotics in patients with schizophrenia. As shown in the response to indication 63 of the first EC meeting, this drug shows affinity and antagonism to 5-HT2c and H1 receptors and these two receptors could be related to the mechanism of weight gain.
As indicated, the incidence of weight gain was observed as adverse event in 20.9% (121/580 cases) and as side effect in 16.9% (85/504 cases) in Japanese clinical studies [Note 1)] and as adverse event in 16.7% (149/894 cases) in overseas long-term studies. Olanzapine has been reported to cause more weight gain than haloperidol. [Notes 3, 4)].
Weight gain is widely recognized as an important risk factor of type II diabetes mellitus. In the overseas clinical studies of this drug, risk factors of more than 200 mg/dl random blood glucose included the more than 10% weight gain and the more than 1 kg/m^2 BMI increase[Note 5)]. Furthermore, there were two cases of diabetes mellitus reported as adverse events in Japanese clinical studes. One was the case with worsening of type II diabetes and the other was the case where a patient at high risk to diabetes because of positive family history, obesity, suspected fatty liver and hyperlipidemia developed to type 2 diabetes with weight gain during the trial. (While she developed weight gain, liver dysfunction, high cholesterol and diabetes in the first year, she started diet therapy and exercise at the 2nd to the 3rd year and her conditions recovered to baseline. Olanzapine was constantly used during this period, and therefore, we think that olanzapine itself is not directly related to observed diabetes mellitus)

As to the incidence of diabetes mellitus, as adverse events, hyperglycemia occurred in 0.64% (16/2,500 cases), diabetes mellitus in 0.64% (16 cases) and diabetic acidosis in 0.04% (1 case) in overseas clinical studies and diabetes mellitus occurred in 0.3% (2/580 cases) in Japanese clinical studies. As to the comparison with haloperidol, the patients with random blood glucose of 200 mg/dl or more accounted for 0.8% (N=4,577) and 0.5% (N=888) after the treatment with olanzapine and haloperidol, respectively in overseas studies. The patients with positeve urine sugar accounted for in none (0%, N=75) and 2.8% (N=72) after the treatment with olanzapine and haloperidol, respectively in Japanese studies [Note 6)]. These results indicated that the incidence of diabetes mellitus during the treatment with olanzapine was as low as below 1% and that there is not a clear difference between olanzapine and haloperidol in the risk of inducing diabetes mellitus.
In summary, olanzapine could cause weight gain and it is thought to cause more weight gain

than haloperidol. Weight gain may trigger the event of diabetes mellitus in the patients with risk factors of diabetes. However, the incidence of diabetes mellitus during the administration of this drug did not reach 1%, indicating not a clear difference in the risk of inducing diabetes mellitus in comparison with haloperidol. With reference to the above, the following changes and additions are made to the Precautions related to the weight gain, hyperglycemia and diabetes mellitus.

2. Important basic precautions (1)As olanzapine may increase body weight, pay attention to obesity, and consider the diet therapy and exercise therapy in patients with diabetes mellitus and those with risk factors of diabetes mellitus (family history of diabetes mellitus, obesity etc.) 4. Adverse reactions (1) Important adverse reactions 3) Hyperglycemia: The events of hyperglycemia could occur. Cases of diabetic coma or diabetic ketoacidosis have been reported.

2) Post-marketing survey

As to the post-marketing survey, we intend to conduct a survey with focus on specific adverse events or side effects whose data could not be collected to the sufficient level in the previous clinical studies.

In other words, we plan to conduct a special survey to investigate the weight gain, hyperglycemia and diabetes mellitus under the clinical application of this drug. As of now, the study is scheduled to be conducted as a special investigation in about 3,000 patients for 6 to 12 months. The safety and efficacy on the patients with the factors which may reduce the clearance (non-smokers, female, elderly) will also be investigated as suggested in level 4-4 question at this time. We intend to contribute to the appropriate use of drugs by publishing the results of this investigation as an academic paper that must be valuable clinical data for Japanese patients.

3)Recent literature, etc.

As already described in the submitted documents before, the mechanism in which carbohydrate metabolism is changed by antipsychotics is unknown at present but the results of studies in animals and healthy adults suggested a decrease in insulin release by antipsychotics. In this regard, the decreased sensitivity of insulin receptors induced by weight gain and obesity through the treatment with antipsychotics, direct action of an antipsychotic on the glucose homeostasis system, indirect action related to prolactin, direct toxicity on the pancreas or interactions of antipsychotics with concomitant drugs are assumed to be associated with the mechanism of insulin release. As to the mechanism to induce hyperglycemia and the relation between hyperglycemia and obesity with focus on olanzapine (mentioned in Level-1-2 this time), we searched the literature in the MEDLINE database from 1996 to September 2000 but no corresponding literature was found. Accordingly, we would like to show the recent literature related to the onset of mechanism

of hyperglycemia in association with antipsychotics in general and the relation between hyperglycemia and obesity, and submit the copy of relevant literature.

Literature related to the effects of antipsychotics on the insulin and plasma glucose of animals and healthy adults

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Literature related to severe hyperglycemia and impaired pancreatic insulin release associated with antipsychotics

12. Fishbein H, Palumbo PJ. 1995. Acute Metabolic Complications in Diabetes. Diabetes in America. 2nd ed. Bethesda: National Institutes of Health. p 283-291.
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Literature related to indirect action related to prolactin

16. Foss MC, Paula FJ, Paccola GM, et al. 1995. Peripheral glucose metabolism in human hyperprolactinemia. Clin Endocrinol 43:721-726.

Literature related to interactions of antipsychotics and concomitant drugs

17. Goldstein LE, Sporn J, Brown S, Kim H, Finkelstein J, Gaffey GK, Stern TA. 1999. New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. Psychosomatics. 40(5): 438-443.

Literature related to weight gain and obesity by antipsychotics in association with the onset of hyperglycemia and diabetes mellitus

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