Report on Investigation Results

July 14, 2026

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name] Olanzapine (oral dosage form)

[Brand names] See Appendix 1.

[Indications] See Appendix 1.

[Dosage and administration] See Appendix 1.

[Marketing authorization holder] See Appendix 1.

[Remarks] Nothing noteworthy

[Investigating office] Office of Pharmacovigilance I

II. Investigation background

Olanzapine is an atypical antipsychotic drug and was approved in Japan in December 2000 for the indication of “schizophrenia” and is also approved for the indication of “improvement of manic symptoms and depressive symptoms in patients with bipolar disorder.” In response to a request for development concerning additional indications submitted by the Japanese Society for Palliative Medicine and Japanese Society of Gastroenterology, the Study Group on Unapproved and Off-label Drugs of High Medical Need and the First Committee on Drugs of the Pharmaceutical Affairs and Food Sanitation Council reviewed and evaluated the request. As a result, the efficacy and safety of olanzapine when used for gastrointestinal symptoms (nausea and vomiting) associated with chemotherapy medicine (such as cisplatin) for cancer (hereinafter referred to as “chemotherapy-induced nausea and vomiting (CINV)”) were deemed to be publicly known in the medical and pharmaceutical fields, and a public knowledge-based application was filed. Consequently, the indication for CINV was also approved.

During the approximately 10-month period after olanzapine was launched in Japan in June 2001, cases of serious hyperglycaemia, diabetic ketoacidosis, and diabetic coma for which a causal relationship between olanzapine and the events was reasonably possible have been reported as adverse reactions. Therefore, the PRECAUTIONS were revised and “patients with diabetes mellitus or a history of diabetes mellitus” was added to the CONTRAINDICATIONS section.

Recently, in response to the request from the Japan Society of Clinical Oncology for exclusion of “patients with diabetes mellitus or a history of diabetes mellitus” from patients to whom olanzapine is

contraindicated when used for CINV based on the following reasons, on April 9, 2026, the Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare (MHLW), requested the Pharmaceuticals and Medical Devices Agency (PMDA) to conduct an investigation into the contraindications of olanzapine ("Notification on Request of Investigation Related to the Safety of Drugs, etc." (PSB/PSD 0409 No. 1)).

- No serious hyperglycaemia-related events have been reported in previously reported clinical studies verifying the efficacy of olanzapine.
- A four-drug antiemetic regimen including olanzapine is specified as the standard antiemetic therapy during high-emetic-risk chemotherapy according to Japanese and overseas guidelines. However, since olanzapine is contraindicated in patients with diabetes mellitus only in Japan, only patients with cancer who have comorbid diabetes mellitus cannot receive a four-drug antiemetic regimen including olanzapine and will experience more severe nausea and vomiting than patients with cancer without diabetes mellitus. This raises a concern about not only distress but also adverse effects on prognosis in patients with cancer who have comorbid diabetes mellitus.

Japan Society of Clinical Oncology has also proposed the following measures as safety measures when olanzapine is used for the indication of CINV in patients with diabetes mellitus:

- Dexamethasone contained in the standard antiemetic therapy for moderate- to high-emetic-risk chemotherapy has a short-term hyperglycaemic effect, and therefore, when chemotherapy is performed in patients with diabetes mellitus, efforts have been made to prevent serious hyperglycaemia-related events such as diabetic ketoacidosis and hyperglycaemic hyperosmolar state; for example, blood glucose levels are monitored on an inpatient basis and insulin is administered depending on the blood glucose levels based on a sliding scale if any abnormalities are observed. When olanzapine is used for the indication of CINV in patients with diabetes mellitus, more careful management will be required than when dexamethasone is used. If the contraindication of olanzapine for CINV in patients with diabetes mellitus is lifted, Japan Society of Clinical Oncology and the Committee for Revision of Guidelines for Proper Use of Antiemetics will issue a statement regarding proper use involving blood glucose control to call attention to safety assurance.

In response to the request for the above investigation, the PMDA decided to discuss the necessity of lifting the contraindication of olanzapine for CINV in "patients with diabetes mellitus or a history of diabetes mellitus".

The PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion were nominated based on their conflict of interest declarations concerning the

relevant products, pursuant to the "Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. Outline of Investigation by the PMDA

1. Background of current contraindication in "patients with diabetes mellitus or a history of diabetes mellitus"

Although no serious adverse events related to glucose metabolism such as diabetic ketoacidosis and diabetic coma were reported in clinical studies of olanzapine in patients with schizophrenia in Japan, precautions concerning hyperglycaemia have been provided in the IMPORTANT PRECAUTIONS section and the Clinically Significant Adverse Reactions section since the approval for the treatment of "schizophrenia" based on the results of overseas clinical studies, etc. However, for approximately 10 months after the launch of olanzapine in Japan in June 2001, 9 cases of adverse reactions including serious hyperglycaemia, diabetic ketoacidosis, and diabetic coma for which a causal relationship between olanzapine and the events was reasonably possible have been reported (including 2 cases of death). Therefore, Dear Healthcare Professional Letters of Emergent Safety Communications (No. 02-1, April 2002) were distributed to facilities including medical institutions in parallel with the revision of PRECAUTIONS to draw attention to diabetic ketoacidosis and diabetic coma resulting from an increase in blood glucose during treatment with olanzapine.

The contents of the revised PRECAUTIONS at that time are as follows. Precautions concerning these events have also been provided for the indications of "improvement of manic symptoms and depressive symptoms in patients with bipolar disorder" and CINV, which were approved after the relevant revision of the PRECAUTIONS.

< Contents of the revised PRECAUTIONS >

- This drug should not be administered to patients with diabetes mellitus or a history of diabetes mellitus. (Added to "CONTRAINDICATIONS".)
- Close monitoring including blood glucose measurements should be performed during treatment with this drug. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures such as administration of insulin preparation should be taken. (inclusion of a precautionary statement in "WARNINGS" section, etc.)
- When this drug is administered, patients and their families should be given a full explanation about the adverse reactions and should be instructed to pay attention to abnormalities such as thirst, excessive drinking, polyuria, and pollakiuria during the treatment and discontinue taking this drug immediately and consult a physician if these symptoms are observed.

(inclusion of a precautionary statement in “WARNINGS” section, etc.)

2. Descriptions in overseas product labeling (US, UK, Europe, Canada, Australia)

The descriptions in overseas product labeling of olanzapine about administration to “Patients with diabetes mellitus or a history of diabetes mellitus” are as follows (see Appendix 2 for details). The indication of CINV has not been approved in any country.

1) Description in the section of contraindications

Administration to “Patients with diabetes mellitus or a history of diabetes mellitus” is not contraindicated in any of the overseas product labeling.

2) Description in other sections than the contraindications section

Country	Description in the product labeling
US	**“WARNINGS AND PRECAUTIONS”** section includes the following detailed descriptions: development and worsening of hyperglycaemia and diabetes mellitus (including ketoacidosis, coma and death) associated with administration of olanzapine have been reported; patients with diabetes mellitus or patients with borderline increased blood glucose levels need to be regularly monitored for blood glucose and hyperglycaemic symptoms before and during the treatment; and increases in blood glucose have been observed in clinical studies.
UK	**“Special warnings and precautions for use”** section includes the following descriptions: development and exacerbation of hyperglycaemia and diabetes mellitus (including ketoacidosis, coma and death) associated with administration of olanzapine have been reported; and patients with diabetes mellitus or patients having the risk factors need to be regularly monitored for blood glucose, weight, and hyperglycaemic symptoms before and during the treatment.
Europe	Same descriptions as UK
Canada	**“WARNINGS AND PRECAUTIONS”** section includes the following descriptions: development and exacerbation of hyperglycaemia and diabetes mellitus (including ketoacidosis, coma and death) associated with administration of olanzapine have been reported; patients with diabetes mellitus or patients having the risk factors need to be regularly monitored for blood glucose, weight, and hyperglycaemic symptoms before and during the treatment; and increased risk of hyperglycaemia has been suggested in clinical studies and epidemiological studies.
Australia	**“SPECIAL WARNINGS AND PRECAUTIONS FOR USE”** section includes the following descriptions: hyperglycaemia (including ketoacidosis, coma and death) associated with administration of olanzapine have been reported; patients with diabetes mellitus or patients having the risk factors need to be regularly monitored

	for blood glucose and hyperglycaemic symptoms before and during the treatment; and increased risk of hyperglycaemia has been suggested in epidemiological studies.

3. Descriptions in clinical practice guidelines issued by academic societies, organizations, etc.

1) Japan Society of Clinical Oncology: Clinical Practice Guidelines for Antiemesis[1]

Olanzapine is recommended to be added to and concomitantly used with the triple combination therapy (5-HT3 receptor antagonist + NK1 receptor antagonist + dexamethasone) as prophylaxis of nausea/vomiting associated with high-emetic-risk chemotherapy. The safety of olanzapine is described as follows.

- Since olanzapine is contraindicated in patients with diabetes mellitus in Japan, conventional triple therapy should be performed in patients with diabetes mellitus.
- The results of a systematic review on increased blood glucose and somnolence, which are representative adverse reactions to olanzapine, showed that the frequency of Grade 2 or higher events was low for both the adverse reactions and no significant difference was observed in the frequency between the olanzapine group and the placebo group, suggesting that addition or concomitant use of olanzapine is considered to cause only minor harm. However, it should be noted that patients with diabetes mellitus were excluded from the clinical studies including olanzapine conducted in Japan.

2) ASCO (American Society of Clinical Oncology): Antiemetics: ASCO Guideline[2]

Olanzapine is described as a drug that is concomitantly used with 5-HT3 receptor antagonist, NK1 receptor antagonist, and dexamethasone as a four-drug antiemetic regimen that is the standard antiemetic therapy for high-emetic-risk chemotherapy. No description on the safety of olanzapine was found.

3) **MASCC/ESMO (Multinational Association of Supportive Care/European Society For Medical Oncology): MASCC/ESMO Antiemetic Guidelines[3]**

Olanzapine is described as a drug that is concomitantly used with 5-HT3 receptor antagonist, NK1 receptor antagonist, and dexamethasone as a four-drug antiemetic regimen that is the standard antiemetic therapy for high-emetic-risk chemotherapy. In the descriptions on the safety of olanzapine, sedation is listed as the most frequent adverse event, but descriptions of adverse events related to glucose metabolism such as hyperglycaemia or administration to patients with diabetes mellitus were not identified.

4) NCCN (National Comprehensive Cancer Network): NCCN Guidelines Antiemesis[4]

---

[1] Japan Society of Clinical Oncology edition: Clinical Practice Guidelines for Antiemesis the third version, revised in October 2023
[2] Hesketh PJ et al. Antiemetic: ASCO Guideline Update. J Clin Oncol 2020;38(24):2782-2797.
[3] MASCC/ESMO antiemetic guideline (2023 update). Multinational Association of Supportive Care in Cancer; 2023.
[4] NCCN Clinical practice guidelines in oncology (NCCN Guidelines) antiemesis. ver 1. 2026. National Comprehensive Cancer Network; 2026.

Olanzapine is described as a drug that is concomitantly used with 5-HT3 receptor antagonist, NK1 receptor antagonist, and dexamethasone as a four-drug antiemetic regimen that is the standard antiemetic therapy for high-emetic-risk chemotherapy. The following descriptions on the safety of olanzapine were found.

- Common adverse reactions include postural hypotension, adverse reactions associated with anticholinergic effects, fatigue, and sedation.
- Olanzapine may be used in patients unsuitable for use of dexamethasone including patients with diabetes mellitus as an alternative to dexamethasone.
- Olanzapine should be administered with care to older adults (US product labeling of olanzapine includes a boxed warning concerning death in patients with dementia-related psychotic symptoms and warnings and precautions concerning type 2 diabetes mellitus and hyperglycaemia).

4. Published literature

The PMDA searched for published reports on clinical studies and observational studies of administration of olanzapine in patients with diabetes mellitus for the indication of CINV using the retrieval conditions listed in Appendix 3. The results are shown below.

1) Randomized comparative study

There were no reported randomized comparative studies involving “patients with diabetes mellitus or a history of diabetes mellitus.” Many overseas randomized comparative studies that evaluated the efficacy of olanzapine for the indication of CINV allow patients with diabetes mellitus with good glycaemic control to participate in the study by excluding only patients with diabetes mellitus that is poorly controlled as per the exclusion criteria instead of uniformly excluding patients with diabetes mellitus, although the number of participants in each study could not be identified.

Among the randomized comparative studies in which patients in either group received olanzapine, hyperglycaemia was reported as an adverse event/adverse reaction in patients treated with olanzapine in some studies, but serious hyperglycaemia-related events such as diabetic ketoacidosis and hyperosmolar hyperglycemic state were not reported in any studies.

2) Observational studies

There was no observational study that investigated the risk of hyperglycaemia associated with olanzapine when olanzapine is administered to “patients with diabetes mellitus or a history of diabetes mellitus” for the indication of CINV. Among observational studies that investigated the impacts of olanzapine on blood glucose levels when administered for the indication of CINV, one study reported that high blood glucose level before the start of

chemotherapy was the risk of increased blood glucose levels after the treatment (Study a. below), while the other study reported that olanzapine had a small impact on casual blood glucose levels regardless of the presence or absence of risk factors of occurrence of diabetes mellitus (Study b. below).

There was no reported study suggesting the causal relationship between olanzapine and serious hyperglycaemia-related events such as diabetic ketoacidosis and hyperosmolar hyperglycemic state.

a. Kanbayashi Y, et al. Factors Contributing to Blood Glucose Elevation Associated With Olanzapine Used as an Antiemetic During Cancer Chemotherapy (In Vivo 2025 ; 39(2) : 902-908)

A single-center, retrospective, observational study on factors contributing to blood glucose elevation associated with use of olanzapine for CINV was conducted. Of the patients who received chemotherapy, 220 patients were included in the analysis after excluding patients who received only 1 course of chemotherapy, patients with diabetes mellitus, and patients who concomitantly used other antipsychotic drugs. Multivariate ordinal logistic regression analysis was performed to identify the factors contributing to blood glucose elevation associated with olanzapine. Factors significantly related to blood glucose elevation associated with olanzapine were casual blood glucose level before the start of chemotherapy (p=0.002), gastric cancer (p=0.003), and use of calcium-channel blockers (p=0.048). In ROC analysis, the casual blood glucose level before chemotherapy of 113 mg/dL or higher was the threshold for predicting elevated blood glucose level of 200 mg/dL or higher after the treatment (sensitivity, 73.8%; specificity, 88.9%; AUC=0.8299).

The listed limitations of this study are retrospective design, single center setting/small sample size, and the inability to completely rule out the possibility of confounding factors and information bias.

b. Tomomatsu T, et al. Effect of the Antiemetic Drug Olanzapine on Blood Sugar Levels in Patients Treated with Adjuvant or Neoadjuvant-Chemotherapy for Breast cancer (Cancer Chemother. 2020 ; 47(10) : 1471-1475)

A retrospective observational study was conducted to evaluate the impacts of olanzapine on blood glucose levels when administered for a short period of time as an antiemetic in the perioperative chemotherapy for breast cancer (AC or CEF therapy). The frequency of diabetic blood glucose levels (casual blood glucose level ≥ 200 mg/dL) and time course of casual blood glucose levels were investigated in 149 breast cancer patients to whom olanzapine was prescribed. Occurrence of diabetic blood

glucose levels was not identified in the patients included in the study during the observation period (median: 3 cycles). In 95 patients whose blood glucose levels were measured at least twice including the measurement before the start of administration of olanzapine, the change in the time course of casual blood glucose levels was small. The same finding was observed even in patients who had risk factors of occurrence of diabetes mellitus such as obesity and high blood pressure. Furthermore, no significant difference was observed in the frequency of increases in casual blood glucose levels to the borderline diabetic blood glucose levels (casual blood glucose level ≥ 140 mg/dL) between before and after administration of olanzapine, regardless of presence or absence of risk factors of the occurrence of diabetes mellitus.

The following limitations are listed for this study: the safety in patients with history of diabetes mellitus or those with high HbA1c levels was not demonstrated because of small number of these patients among patients treated with olanzapine; the detailed dietary status before measurement of casual blood glucose levels has not been clearly investigated; and rate of medication compliance in patients treated with olanzapine has not been investigated.

5. Adverse reaction case reports in Japan after the marketing approval

Of the Japanese cases of adverse reactions to olanzapine reported to the PMDA by May 31, 2026, adverse reactions related to glucose metabolism (SMQ: Hyperglycaemia/new onset diabetes mellitus [narrow]) that occurred in patients for whom events related to diabetes mellitus are listed in the column for “Underlying diseases/complications/past history” were 98 events in 91 cases.

Of these, adverse reactions (PT) in 2 cases in which olanzapine was considered to be administered for the indication of CINV were 1 event of “hyperglycaemic hyperosmolar nonketotic syndrome” and “diabetes mellitus” in 1 case each (See Appendix 4).

In the case of “hyperglycaemic hyperosmolar nonketotic syndrome” (No. 2 in Appendix 4), olanzapine and dexamethasone administered as antiemetics for treatment with antineoplastic agents were considered to have increased blood glucose levels, leading to hyperglycaemic hyperosmolar nonketotic syndrome. In this case, blood glucose levels were not measured before and during treatment with olanzapine.

6. Research reports and reports on measures taken overseas

Of the research reports and reports on measures taken overseas reported to the PMDA by May 31, 2026, there were no reports on administration to “patients with diabetes mellitus or a history of diabetes mellitus” for the indication of CINV.

7. PMDA's judgment based on the results of investigation

Although clinical experience with olanzapine in "patients with diabetes mellitus or a history of diabetes mellitus" for CINV is limited in Japan, as a result of the investigation described in the above 1. to 6., the PMDA judged as follows for the reasons described below: "Patients with diabetes mellitus or a history of diabetes mellitus" may be deleted from the "CONTRAINDICATIONS" section for the indication of CINV on condition that the risks of serious hyperglycaemia-related events including diabetic ketoacidosis and hyperosmolar hyperglycemic state are minimized by such measures as providing administration of olanzapine on an inpatient basis, limiting the administration to patients with diabetes mellitus with good glycaemic control, administering olanzapine in a healthcare setting capable of adequately responding to emergencies throughout the administration period, and monitoring blood glucose before initiation of treatment and frequently every day during treatment with olanzapine (see Appendix 5). (Appendix 5 is not included in this document. See the detailed information on revisions of PRECAUTIONS.)

- Although there were no randomized comparative studies involving "patients with diabetes mellitus or a history of diabetes mellitus" and no observational studies that investigated the risks of hyperglycaemia when olanzapine is administered to "patients with diabetes mellitus or a history of diabetes mellitus," many overseas randomized comparative studies that investigated the efficacy of olanzapine allow patients with diabetes mellitus with good glycaemic control to participate in the study instead of excluding patients with diabetes mellitus uniformly.
- Among the randomized comparative studies in which patients in either group received olanzapine for CINV, hyperglycaemia was reported as an adverse event/adverse reaction in patients treated with olanzapine in some studies, but serious hyperglycaemia-related events such as diabetic ketoacidosis and hyperosmolar hyperglycemic state were not reported in any studies.
- The adverse reaction reports after the marketing approval in Japan include a case of "Hyperglycaemic hyperosmolar nonketotic syndrome" in a patient with history of type 2 diabetes mellitus who received olanzapine for the indication of CINV. In the relevant case, however, blood glucose was not monitored before and during the treatment with olanzapine, which may have led to a delay in detection of hyperglycaemia and resulted in progression to a severe condition. Monitoring of blood glucose levels before, during, and after the treatment with olanzapine is considered to enable early detection of increased blood glucose, thereby reducing the risks of serious hyperglycaemia-related events.
- In light of the blood glucose control method in the current standard antiemetic therapy

containing dexamethasone presented by Japan Society of Clinical Oncology, it is considered that the risks of serious hyperglycaemia-related events can be minimized by controlling blood glucose levels based on the proposed revised contents of the package insert (Appendix 5), which requires healthcare professionals to not only perform blood glucose monitoring before, during and after the administration of olanzapine but also limit the administration to patients with good glycaemic control and use the minimum necessary dosage and administration duration of olanzapine.

- In the overseas product labeling and overseas guidelines for antiemetic therapy, olanzapine is not contraindicated in “patients with diabetes mellitus or a history of diabetes mellitus”.

As per the request and opinions on the safety measures of Japan Society of Clinical Oncology, if the contraindication of olanzapine for CINV in “patients with diabetes mellitus or a history of diabetes mellitus” is lifted, it is important to issue a statement regarding proper use involving blood glucose control at Japan Society of Clinical Oncology to call attention to safety assurance. Furthermore, since Japan Society of Clinical Oncology is planning to conduct a survey on the safety in terms of blood glucose control, etc. after the lifting of the contraindication, it is necessary to evaluate the impact of this lifting taking the relevant survey results into account.

IV. Expert Discussion

1. Necessity of lifting the contraindication of olanzapine for CINV in “patients with diabetes mellitus or a history of diabetes mellitus” evaluated in this discussion

The judgment of the PMDA on the lifting of the contraindication of olanzapine for CINV in “patients with diabetes mellitus or a history of diabetes mellitus” was supported by all the expert advisors.

2. Precautions concerning use of olanzapine for CINV in “patients with diabetes mellitus or a history of diabetes mellitus” after the lifting of the relevant contraindication

All the expert advisors supported the policy to provide the precautions according to the revised contents of the package insert proposed based on the PMDA's judgment as shown in Appendix 5.

3. Other opinions

In addition to the above, the expert advisors provided the following opinions:

- As for the measures such as blood glucose control based on a sliding scale, cooperation with endocrinologists and diabetologists is necessary depending on the case.
- Since patients with diabetes mellitus were excluded from Japanese clinical studies of

olanzapine for CINV, it is necessary to continue to collect data on how serious hyperglycaemia will occur with co-administration with dexamethasone.

The PMDA considers that, in the event that measures are taken to lift the relevant contraindication, the above opinions should be taken into account in the activities to call attention to the safety assurance, such as issuing a statement on proper use involving blood glucose control, and in the survey on the safety in terms of blood glucose control, etc. that the Japan Society of Clinical Oncology plans to conduct after the lifting of the contraindication.

V. Overall evaluation

The PMDA concluded that PRECAUTIONS may be revised according to Appendix 5 based on the above discussions.

End of the document

Appendix 1

Summary of investigated drug products (as of April 27, 2026)

No	Brand name	Marketing authorization holder	Indications/dosage and administration
1	Zyprexa tablets 2.5 mg, 5 mg, 10 mg, Zyprexa Zydis tablets 2.5 mg, 5 mg, 10 mg, Zyprexa fine granule 1%	CHEPLAPHARM K.K.	Indications ○ Schizophrenia ○ Improvement of manic symptoms and depressive symptoms in patients with bipolar disorder ○ Gastrointestinal symptoms (nausea and vomiting) associated with chemotherapy medicine (such as cisplatin) for cancer Dosage and administration < Schizophrenia > The usual starting dose for adults is 5 to 10 mg of olanzapine orally administered once daily. The maintenance dose is 10 mg orally administered once daily. The dose may be adjusted according to the patient's age and symptoms as appropriate. However, the daily dose should not exceed 20 mg. < Improvement of manic symptoms in patients with bipolar disorder > The usual starting dose for adults is 10 mg of olanzapine orally administered once daily. The dose may be adjusted according to the patient's age and symptoms as appropriate, but the daily dose
2	OLANZAPINE OD Tablets 2.5 mg "VTRS," 5 mg "VTRS," 10 mg "VTRS"	Viatris Healthcare G.K.	
3	Olanzapine Tablets 1.25 mg "AMEL," 2.5 mg "AMEL," 5 mg "AMEL," 10 mg "AMEL," 20 mg "AMEL," Olanzapine OD Tablets 1.25 mg "AMEL," 2.5 mg "AMEL," 5 mg "AMEL," 10 mg "AMEL," Olanzapine Fine Granules 1% "AMEL"	Kyowa Pharmaceutical Industry Co., Ltd.	
4	OLANZAPINE Tablets 2.5 mg "KYORIN," 5 mg "KYORIN," 10 mg "KYORIN," OLANZAPINE OD Tablets 2.5 mg "KYORIN," 5 mg "KYORIN," 10 mg "KYORIN," OLANZAPINE Fine Granules 1% "KYORIN"	KYORIN Rimedio Co., Ltd.	

5	OLANZAPINE Tablets 2.5 mg [SAWAI], 5 mg [SAWAI], 10 mg [SAWAI], OLANZAPINE Fine Granules 1% [SAWAI]	Sawai Pharmaceutical Co., Ltd.	should not exceed 20 mg. < Improvement of depressive symptoms in patients with bipolar disorder > The usual starting dose for adults is 5 mg of olanzapine orally administered once daily. Thereafter, the dose is increased to 10 mg once daily. Both doses should be given before bedtime. The dose may be adjusted according to the patient's age and symptoms as appropriate, but the daily dose should not exceed 20 mg. < Gastrointestinal symptoms (nausea and vomiting) associated with chemotherapy medicine (such as cisplatin) for cancer > The usual dose for adults is 5 mg of olanzapine orally administered once daily when co-administered with other antiemetics. The dose may be adjusted according to the patient's age and symptoms as appropriate, but the daily dose should not exceed 10 mg.
6	OLANZAPINE TABLETS 2.5 mg “DSEP”, 5 mg “DSEP”, 10 mg “DSEP”, OLANZAPINE OD TABLETS 2.5 mg “DSEP”, 5 mg “DSEP”, 10 mg “DSEP”, OLANZAPINE FINE GRANULES 1% “DSEP”	Daiichi Sankyo Espha Co., Ltd.	
7	Olanzapine OD Tablets 2.5 mg “TAKATA,” 5 mg “TAKATA,” 10 mg “TAKATA,” Olanzapine fine granules 1% “TAKATA”	TAKATA Pharmaceutical Co., Ltd.	
8	OLANZAPINE TABLETS 2.5 mg “TOWA,” 5 mg “TOWA,” 10 mg “TOWA,” OLANZAPINE OD TABLETS 2.5 mg “TOWA,” 5 mg “TOWA,” 10 mg “TOWA,” OLANZAPINE FINE GRANULES 1% “TOWA”	Towa Pharmaceutical Co., Ltd.	
9	Olanzapine OD Tablets 2.5 mg “Nichi-	Nichi-Iko Pharmaceutical Co.,	

	Iko,” 5 mg “Nichi-Iko,” 10 mg “Nichi-Iko,” Olanzapine Fine Granules 1% “Nichi-Iko”	Ltd.	
10	Olanzapine Tablets 2.5 mg “NIG,” 5 mg “NIG,” 10 mg “NIG,” Olanzapine OD Tablets 2.5 mg “NIG,” 5 mg “NIG,” 10 mg “NIG,”	Nichi-Iko Pharmaceutical Co., Ltd. Gifu Plant	
11	Olanzapine Tablets 2.5 mg “NISSIN,” 5 mg “NISSIN,” 10 mg “NISSIN,” Olanzapine Fine Granules 1% “NISSIN”	Nissin Pharmaceutical Co., Ltd.	
12	Olanzapine Tablets 2.5 mg “Nipro,” 5 mg “Nipro,” 10 mg “Nipro,” Olanzapine OD Tablets 2.5 mg “Nipro,” 5 mg “Nipro,” 10 mg “Nipro,” Olanzapine Fine Granules 1% “Nipro”	Nipro Corporation	
13	Olanzapine Tablets 2.5 mg “NP,” 5 mg “NP,” 10 mg “NP,” Olanzapine OD Tablets 5 mg “NP,” 10 mg “NP,” Olanzapine Fine Granules 1% “NP”	Nipro Corporation	
14	Olanzapine OD Tablets 2.5 mg “JG,” 5 mg “JG,” 10 mg “JG”	Nihon Generic Co., Ltd.	
15	OLANZAPINE Tablets 2.5 mg	Meiji Seika Pharma Co., Ltd.	

	“MEIJI,” 5 mg “MEIJI,” 10 mg “MEIJI,” OLANZAPINE OD Tablets 2.5 mg “MEIJI,” 5 mg “MEIJI,” 10 mg “MEIJI,” OLANZAPINE Fine granules 1% “MEIJI”		
16	OLANZAPINE TABLETS 2.5 mg “YD,” 5 mg “YD,” 10 mg “YD”	Yoshindo Holdings Inc.	

Appendix 2

Descriptions in overseas product labeling regarding administration to “Patients with diabetes mellitus or a history of diabetes mellitus”

1. Descriptions in the US product labeling

Brand name: ZYPREXA
Version as of January 30, 2026
5 WARNINGS AND PRECAUTIONS **5.5 Metabolic Changes** (omitted) **Hyperglycemia and Diabetes Mellitus** Healthcare providers should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug [see Patient Counseling Information (17)]. Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical

Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the 2 highest serum concentrations was 15.0 mg/dL.

In a study of healthy volunteers, subjects who received olanzapine (N=22) for 3 weeks had a mean increase compared to baseline in fasting blood glucose of 2.3 mg/dL. Placebo-treated subjects (N=19) had a mean increase in fasting blood glucose compared to baseline of 0.34 mg/dL.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse reactions, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose level ≥126 mg/dL).

Olanzapine-treated patients had a greater mean HbA1c increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA1c decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

In an analysis of 8 placebo-controlled studies (median treatment exposure 4-5 weeks), 6.1% of olanzapine-treated subjects (N=855) had treatment-emergent glycosuria compared to 2.8% of placebo-treated subjects (N=599). Table 2 shows short-term and long-term changes in fasting glucose levels from adult olanzapine monotherapy studies.

Table 2: Changes in Fasting Glucose Levels from Adult Olanzapine Monotherapy Studies

			Up to 12 weeks exposure		**At least 48 weeks exposure**	
Laboratory Analyte	**Category Change (at least one) from Baseline**	**Treatment Arm**	**N**	**Patients**	**N**	**Patients**
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Olanzapine	543	2.2%	345	12.8%
		Placebo	293	3.4%	NA[a]	NA[a]
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Olanzapine	178	17.4%	127	26.0%
		Placebo	96	11.5%	NA[a]	NA[a]

[a] Not Applicable.

The mean change in fasting glucose for patients exposed at least 48 weeks was 4.2 mg/dL (N=487). In analyses of patients who completed 9-12 months of olanzapine therapy, mean change in fasting and nonfasting glucose levels continued to increase over time.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of ZYPREXA RELPREVV have not been established in patients under the age of 18 years.

In an analysis of 3 placebo-controlled oral olanzapine monotherapy studies of adolescent patients (13-17 years), including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a greater mean change from baseline in fasting glucose levels compared to placebo (2.68 mg/dL versus 2.59 mg/dL). The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (N=121). Table 3 shows short-term and long-term changes in fasting blood glucose from adolescent oral olanzapine monotherapy studies.

Table 3: Changes in Fasting Glucose Levels from Adolescent Oral Olanzapine Monotherapy Studies

			Up to 12 weeks exposure		**At least 48 weeks exposure**	
Laboratory Analyte	**Category Change (at least one) from Baseline**	**Treatment Arm**	**N**	**Patients**	**N**	**Patients**
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Olanzapine	124	0%	108	0.9%
		Placebo	53	1.9%	NA[a]	NA[a]
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Olanzapine	14	14.3%	13	23.1%
		Placebo	13	0%	NA[a]	NA[a]

[a] Not Applicable.

2. Descriptions in the UK product labeling

Brand name: ZYPREXA

Version as of April 14, 2026
4.4 Special warnings and precautions for use (omitted) **Hyperglycaemia and diabetes** Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported uncommonly, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines, e.g. measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter. Patients treated with any antipsychotic medicines, including ZYPREXA, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly, e.g. at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.

3. Descriptions in the European product labeling

Brand name: ZYPREXA
Version as of February 27, 2026
4.4 Special warnings and precautions for use (omitted) **Hyperglycaemia and diabetes** Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported uncommonly, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines, e.g. measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter. Patients treated with any antipsychotic medicines, including ZYPREXA, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors

for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly, e.g. at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.

4. Descriptions in the Canadian product labeling

Brand name: ZYPREXA
Version as of January 30, 2025
7 WARNINGS AND PRECAUTIONS (omitted) **<u>Endocrine and Metabolism</u>** <u>Hyperglycaemia:</u> As with some other antipsychotics, exacerbation of pre-existing diabetes and hyperglycaemia have been reported rarely and diabetic ketoacidosis and diabetic coma including some fatal cases have been reported very rarely during the use of ZYPREXA, sometimes in patients with no reported history of hyperglycaemia (see 8 ADVERSE REACTIONS; Post-Market Adverse Drug Reactions section). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Patients should have baseline and periodic monitoring of blood glucose and body weight. In clinical trials (up to 52 weeks) olanzapine was associated with a greater mean change in glucose relative to placebo. Treatment-emergent clinically significant changes in fasting glucose were observed in patients with or without evidence of glucose dysregulation at baseline (see 8 ADVERSE REACTIONS, Other Adverse Events Observed During Clinical Trials with Oral and Intramuscular Olanzapine Across All Indications, Glucose Changes). Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and

weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

5. Descriptions in the Australian product labeling

Brand name: ZYPREXA
Version as of October 14, 2025
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE (omitted) **Hyperglycaemia and diabetes mellitus** Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including ZYPREXA. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with

atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Appendix 3

Published literature retrieval conditions

Of the reports searched for under the following conditions (1) to (3) (date of search: April 13, 2026), the reports that were considered by the PMDA to include descriptions concerning the safety of olanzapine when used for the indication of CINV in patients with cancer complicated by diabetes mellitus were reviewed.

(1) 47 reports on randomized comparative studies searched using PubMed with search formula [Olanzapine[Mesh] and ("Neoplasms/drug therapy"[Mesh] OR nausea/prevention and control[Mesh] OR vomiting/prevention and control[Mesh]) and "randomized controlled trial"[pt]].

(2) 2 reports searched using PubMed with search formula [Olanzapine[Mesh] and ("Neoplasms/drug therapy"[Mesh] OR nausea/prevention and control[Mesh] OR vomiting/prevention and control[Mesh]) and ("Glucose Metabolism Disorders/chemically induced"[Mesh] OR "Diabetes Mellitus"[Mesh])].

(3) 15 reports searched using Ichushi with the search formula [(diabetes mellitus/TH OR diabetes mellitus/AL OR hyperglycaemia/TH OR hyperglycaemia/AL OR glucose metabolism abnormal/TH OR glucose metabolism abnormal/AL) AND ((olanzapine/TH OR olanzapine/AL) OR (olanzapine/TH OR olanzapine/AL)) AND ((adverse reaction/TH OR adverse reaction/AL) OR (adverse event/TH OR adverse event/AL) OR (safety/TH OR safety/AL)) AND ((tumour/TH OR tumour/AL) OR (nausea/TH OR nausea/AL) OR (vomiting/TH OR vomiting/AL) OR (antiemetic/TH OR antiemetic/AL)) AND PT=original paper].

Appendix 4

List of cases with serious adverse reactions in Japan *

No.	Year of onset	Age	Sex	Underlying diseases/ complications/ past history	Adverse reaction (PT)	Outcome	Daily dose of olanzapine	Period between administration and onset	Treatment for the adverse reactions
1	2025	40s	Male	Gastric cancer, diabetes mellitus	Diabetes mellitus	Unknown	Unknown	Unknown	Dose reduction of olanzapine
2	2025	56	Male	Malignant tongue cancer, type 2 diabetes mellitus, dyslipidaemia, alcohol use, tobacco user	Dehydration	Unknown	5 mg	31 days	Fluid administration, insulin administration
					Altered state of consciousness	Unknown		31 days	
					Hyperglycaemic hyperosmolar nonketotic syndrome	Unknown		31 days	
					Intestinal ischaemia	Unknown		31 days	

* Of reported cases of adverse reactions related to glucose metabolism (SMQ: Hyperglycaemia/new onset diabetes mellitus [narrow]) that occurred in patients for whom events related to diabetes mellitus are listed in the column for “Underlying diseases/complications/past history”, cases for which olanzapine was considered to have been administered for the indication of CINV.