Review Report

November 13, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical products submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Names

(1) Zyprexa Tablets 2.5 mg
(2) Zyprexa Tablets 5 mg
(3) Zyprexa Tablets 10 mg
(4) Zyprexa Fine Granules 1%
(5) Zyprexa Zydis Tablets 2.5 mg
(6) Zyprexa Zydis Tablets 5 mg
(7) Zyprexa Zydis Tablets 10 mg
(8) Olanzapine Tablets 2.5 mg "DSEP"
(9) Olanzapine Tablets 5 mg "DSEP"
(10) Olanzapine Tablets 10 mg "DSEP"
(11) Olanzapine Fine Granules 1% "DSEP"
(12) Olanzapine OD Tablets 2.5 mg "DSEP"
(13) Olanzapine OD Tablets 5 mg "DSEP"
(14) Olanzapine OD Tablets 10 mg "DSEP"
(15) Olanzapine Tablets 2.5 mg "Nichi-Iko"
(16) Olanzapine Tablets 5 mg "Nichi-Iko"
(17) Olanzapine Tablets 10 mg "Nichi-Iko"
(18) Olanzapine Fine Granules 1% "Nichi-Iko"
(19) Olanzapine OD Tablets 2.5 mg "Nichi-Iko"
(20) Olanzapine OD Tablets 5 mg "Nichi-Iko"
(21) Olanzapine OD Tablets 10 mg "Nichi-Iko"
(22) Olanzapine Fine Granules 1% "Pfizer"
(23) Olanzapine Tablets 2.5 mg "Nipro"
(24) Olanzapine Tablets 5 mg "Nipro"
(25) Olanzapine Tablets 10 mg "Nipro"
(26) Olanzapine Fine Granules 1% "Nipro"
(27) Olanzapine OD Tablets 5 mg "Nipro"
(28) Olanzapine OD Tablets 10 mg "Nipro"
(29) Olanzapine Tablets 2.5 mg "Pfizer"

(30) Olanzapine Tablets 5 mg "Pfizer"
(31) Olanzapine Tablets 10 mg "Pfizer"
(32) Olanzapine OD Tablets 2.5 mg "Pfizer"
(33) Olanzapine OD Tablets 5 mg "Pfizer"
(34) Olanzapine OD Tablets 10 mg "Pfizer"

Non-proprietary Name Olanzapine (JAN*)

Applicants (1) to (7): Eli Lilly Japan K.K.
(8) to (14): Daiichi Sankyo Espha Co., Ltd.
(15) to (21): Nichi-Iko Pharmaceutical Co., Ltd.
(22): Mylan Seiyaku Ltd.
(23) to (28): Nipro Corporation
(29) to (34): Daito Pharmaceutical Co., Ltd.

Dates of Application (1) to (7): June 22, 2017
(8) to (14): July 6, 2017
(15) to (18), (20) to (28): July 7, 2017
(19): August 22, 2017
(29) to (34): July 28, 2017

Dosage Form/Strength (1)(2)(3)(8)(9)(10)(15)(16)(17)(23)(24)(25)(29)(30)(31):
Each tablet contains 2.5, 5, or 10 mg of Olanzapine.
(4)(11)(18)(22)(26):
Each 1 g of fine granules contains 10 mg of Olanzapine.
(5)(6)(7)(12)(13)(14)(19)(20)(21)(27)(28)(32)(33)(34):
Each orally disintegrating tablet contains 2.5, 5, or 10 mg of Olanzapine.

Application classification Prescription drugs (4) Drugs with a new indication, and (6) Drugs with a new dosage

Items Warranting Special Mention

Application based on “Preliminary Evaluation by the Pharmaceutical Affairs and Food Sanitation Council” (PSEHB/PED Notification No. 0609-3 dated June 9, 2017, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare [MHLW])

Expedited review based on “Review process for new drugs subjected to preliminary evaluation by the Pharmaceutical Affairs and Food Sanitation Council” (PFSB/ELD Notification No. 0915-3 dated September 15, 2010, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW)

Reviewing Office Office of New Drug I

Results of Review

The First Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council, in its meeting held on June 9, 2017, made a preliminary evaluation of "Report on Eligibility for Public Knowledge-Based Applications: Olanzapine - Gastrointestinal Symptoms (nausea, vomiting) Associated with Antineoplastic Agents, by Study Group on Unapproved and Off-label Drugs of High Medical Need." On the basis of the preliminary evaluation and the data submitted, PMDA has concluded that the products have efficacy and safety in the treatment of gastrointestinal symptoms (nausea, vomiting) associated with antineoplastic agents (e.g., cisplatin) (see Attachment).

As a result of its review, PMDA has concluded that the products may be approved for the indications and dosage and administration shown below.

Indications

Schizophrenia

Improvement of manic and depressive symptoms associated with bipolar disorder

Gastrointestinal symptoms (nausea, vomiting) associated with antineoplastic agents (e.g., cisplatin)

(Underline denotes additions.)

Dosage and Administration

Schizophrenia:

The usual starting dose for adults is 5 to 10 mg of Olanzapine orally once daily. The maintenance dose is 10 mg orally once daily. The dosage may be adjusted according to age and symptoms, but the daily dose should not exceed 20 mg.

Improvement of manic symptoms associated with bipolar disorder:

The usual starting dose for adults is 10 mg of Olanzapine orally once daily. The dosage may be adjusted according to age and symptoms, but the daily dose should not exceed 20 mg.

Improvement of depressive symptoms associated with bipolar disorder:

The usual starting dose for adults is 5 mg of Olanzapine orally once daily. The dose is then increased to 10 mg once daily. The drug should be taken before going to bed. The dosage may be adjusted according to age and symptoms, but the daily dose should not exceed 20 mg.

Gastrointestinal symptoms (nausea, vomiting) associated with antineoplastic agents (e.g., cisplatin):

In combination with other antiemetic agents, the usual adult dose is 5 mg of Olanzapine orally once daily. The dosage may be increased according to the patient's condition, but the daily dose should not exceed 10 mg.

(Underline denotes additions.)

**Japanese Accepted Name (modified INN)*

Attachment

Review Report

November 13, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Products Submitted for Approval

Brand Names

(1) Zyprexa Tablets 2.5 mg
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(3) Zyprexa Tablets 10 mg
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Non-proprietary Name	Olanzapine
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	(8) to (14): Daiichi Sankyo Espha Co., Ltd.
	(15) to (21): Nichi-Iko Pharmaceutical Co., Ltd.
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Dosage Form/Strength	(1)(2)(3)(8)(9)(10)(15)(16)(17)(23)(24)(25)(29)(30)(31): Each tablet contains 2.5, 5, or 10 mg of Olanzapine. (4)(11)(18)(22)(26): Each 1 g of fine granules contains 10 mg of Olanzapine. (5)(6)(7)(12)(13)(14)(19)(20)(21)(27)(28)(32)(33)(34): Each orally disintegrating tablet contains 2.5, 5, or 10 mg of Olanzapine.

Proposed Indications

Schizophrenia

Improvement of manic and depressive symptoms associated with bipolar disorder

Gastrointestinal symptoms (nausea, vomiting) associated with antineoplastic agents (e.g., cisplatin)

(Underline denotes additions.)

Proposed Dosage and Administration

Schizophrenia:

The usual starting dose for adults is 5 to 10 mg of Olanzapine orally once daily. The maintenance dose is 10 mg orally once daily. The dosage may be adjusted according to age and symptoms, but the daily dose should not exceed 20 mg.

Improvement of manic symptoms associated with bipolar disorder:

The usual starting dose for adults is 10 mg of Olanzapine orally once daily. The dosage may be adjusted according to age and symptoms, but the daily dose should not exceed 20 mg.

Improvement of depressive symptoms associated with bipolar disorder:
The usual starting dose for adults is 5 mg of Olanzapine orally once daily. The dose is then increased to 10 mg once daily. The drug should be taken before going to bed. The dosage may be adjusted according to age and symptoms, but the daily dose should not exceed 20 mg.

Gastrointestinal symptoms (nausea, vomiting) associated with antineoplastic agents (e.g., cisplatin):
In combination with other antiemetic agents, the usual adult dose is 5 mg of Olanzapine orally once daily. The dosage may be increased according to the patient's condition, but the daily dose should not exceed 10 mg.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Antineoplastic agents including cisplatin enhance the secretion of serotonin (hereafter 5-HT) from enterochromaffin cells in the gastrointestinal mucosa, thereby stimulating the vomiting center; this causes chemotherapy-induced nausea and vomiting (hereafter CINV). According to several reports, antineoplastic agents enhance the secretion of substance P in enterochromaffin cells in the intestinal mucosa, thereby inducing the binding of substance P to central nervous system neurokinin 1 (hereafter NK_1) receptors; this also induces CINV (*Drug Metab Dispos*. 2003;31:785-791; *Neuropharmacology*. 1996;35:1121-1129; *Neuropharmacology*. 1993;32:799-806). As CINV is a cause of discontinuation of chemotherapy, antiemetic therapy is necessary.

Olanzapine has a high affinity for dopamine receptors, 5-HT receptors, and histamine H1 receptors. In Japan, olanzapine was approved for the indications of schizophrenia in December 2000, improvement of manic symptoms associated with bipolar disorder in October 2010, and improvement of depressive symptoms associated with bipolar disorder in February 2012.

The US guidelines "NCCN Clinical practice guidelines in oncology (NCCN Guidelines) antiemesis. ver. 2. 2017" and European guideline "MASCC/ESMO antiemetic guideline 2016" (Multinational Association of Supportive Care in Cancer [MASCC]; 2016) recommend the addition of olanzapine to the 3-drug regimen of a corticosteroid, a $5\text{-}HT_3$ receptor antagonist, and an NK_1 receptor antagonist, as a therapeutic option for CINV. In the Japanese guidelines "Guidelines for the Proper Use of Antiemetics; October 2015 (2nd Edition)" (Compiled by the Japan Society of Clinical Oncology), olanzapine is positioned as an adjuvant antiemetic on the basis of the US and other guidelines.

In view of these circumstances, the Japanese Society for Palliative Medicine and the Japanese Society of Gastroenterology submitted a request for the development of olanzapine for the additional indication of gastrointestinal symptoms (nausea, vomiting) associated with antineoplastic agents. The Study Group on Unapproved and Off-label Drugs of High Medical Need (hereafter Study Group) discussed the request and concluded that there were high medical needs for olanzapine for the indication. MHLW thus issued a request for the development of olanzapine. Subsequently, Study Group compiled the "Report on Eligibility for Public Knowledge-Based Applications: Olanzapine - Gastrointestinal Symptoms (nausea, vomiting) Associated with Antineoplastic Agents, by Study Group on Unapproved and Off-label Drugs of High Medical Need." In its meeting held on June 9, 2017, the First Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council made a preliminary evaluation based on the report by Study Group, and concluded that there was no problem in submitting a public knowledge-based application for the additional indication (gastrointestinal symptoms [nausea, vomiting) associated with the use of antineoplastic agents) and its dosage and administration.

The present application is based on "Preliminary Evaluation by the Pharmaceutical Affairs and Food Sanitation Council" (PSEHB/PED Notification No. 0609-3 dated June 9, 2017) and "Q&A on Off-Label Use of Drugs Subjected to the Preliminary Evaluation Regarding Public Knowledge-Based Application

by the Pharmaceutical Affairs and Food Sanitation Council" (Administrative Notice dated September 1, 2010, by the General Affairs Division, Evaluation and Licensing Division, and Safety Division of Pharmaceutical and Food Safety Bureau, MHLW).

In the present review process, the Expert Discussion was omitted based on "Review process for new drugs subjected to preliminary evaluation by the Pharmaceutical Affairs and Food Sanitation Council" (PFSB/ELD Notification No. 0915-3 dated September 15, 2010). This review report was therefore compiled without the Expert Discussion.

2. Clinical Data and Outline of the Review Conducted by PMDA

For the present application, no new clinical studies were conducted. The application data submitted consisted of "Report on Eligibility for Public Knowledge-Based Applications: Olanzapine - Gastrointestinal Symptoms (nausea, vomiting) Associated with Antineoplastic Agents, by Study Group on Unapproved and Off-label Drugs of High Medical Need," the package insert (draft), and other materials.

2.R Outline of the review conducted by PMDA

2.R.1 Indication

Based on the preliminary evaluation (made at a meeting held on June 9, 2017) by the First Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council, PMDA concluded the following indication was appropriate: "Gastrointestinal symptoms (nausea, vomiting) associated with antineoplastic agents (e.g., cisplatin)." PMDA also concluded that the following statement should be included in the Precautions for Indications section: "Olanzapine should be used only in patients treated with antineoplastic agents (e.g., cisplatin) causing severe nausea or vomiting."

2.R.2 Dosage and administration

Based on the preliminary evaluation (made at a meeting held on June 9, 2017) by the First Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council, PMDA concluded that the proposed dosage and administration were appropriate. PMDA also concluded that the following statements should be included in the Precautions for Dosage and Administration section:

- "In principle, olanzapine is used in combination with a corticosteroid, a 5-HT_3 receptor antagonist, and a NK_1 receptor antagonist. The dosage of concomitant corticosteroids, 5-HT_3 receptor antagonists, and NK_1 receptor antagonists should be determined based on the latest information, including data in the package inserts for the individual agents."
- "In principle, olanzapine is administered before the beginning of treatment with antineoplastic agents. In general, olanzapine should not be administered for more than 6 days in each chemotherapy cycle."

2.R.3 Elevation of blood glucose levels

Olanzapine has been reported to elevate blood glucose levels, thereby causing diabetic ketoacidosis and diabetic coma. Therefore, the current package insert for olanzapine (in the Warnings and Important Precautions sections) include the following precautionary statements:

- Patients on olanzapine therapy should be carefully monitored through blood glucose testing and other measures. Healthcare professionals should instruct patients to pay attention to abnormal symptoms such as thirst, polydipsia, polyuria, and pollakiuria, and to immediately discontinue olanzapine and consult a physician if such symptoms occur.

Such care should be taken also in patients receiving olanzapine for the treatment of gastrointestinal symptoms (nausea, vomiting) associated with antineoplastic agents.

3. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

The applicant submitted the present application without conducting any new studies, on the grounds that information on the proposed indication was already publicly available in the medical and pharmaceutical fields, based on "Preliminary Evaluation by the Pharmaceutical Affairs and Food Sanitation Council" (PSEHB/PED Notification No. 0609-3 dated June 9, 2017). Accordingly, there were no data to be assessed for compliance.

4. Overall Evaluation during Preparation of the Review Report

The First Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council, in its meeting held on June 9, 2017, made a preliminary evaluation of "Report on Eligibility for Public Knowledge-Based Applications: Olanzapine - Gastrointestinal Symptoms (nausea, vomiting) Associated with Antineoplastic Agents, by Study Group on Unapproved and Off-label Drugs of High Medical Need." On the basis of the preliminary evaluation and PMDA's review described above, PMDA has concluded that the products may be approved for the indications and dosage and administration shown below.

Indications

Schizophrenia

Improvement of manic and depressive symptoms associated with bipolar disorder

<u>Gastrointestinal symptoms (nausea, vomiting) associated with antineoplastic agents (e.g., cisplatin)</u>

(Underline denotes additions.)

Dosage and Administration

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The usual starting dose for adults is 5 to 10 mg of Olanzapine orally once daily. The maintenance dose is 10 mg orally once daily. The dosage may be adjusted according to age and symptoms, but the daily dose should not exceed 20 mg.

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In combination with other antiemetic agents, the usual adult dose is 5 mg of Olanzapine orally once daily. The dosage may be increased according to the patient's condition, but the daily dose should not exceed 10 mg.

(Underline denotes additions.)

Appendix

List of Abbreviations

CINV	Chemotherapy Induced Nausea and Vomiting
PMDA	Pharmaceuticals and Medical Devices Agency
Study Group	Study Group on Unapproved and Off-label Drugs of High Medical Need
5-HT	5-hydroxytryptamine/serotonin
NK	Neurokinin