**Revised: October 2003 (5th version)
*Revised: July 2002

Standard Commodity Classification No. of Japan
871179

- Antipsychotic agent -

Zyprexa® Tablets 2.5 mg
Zyprexa® Tablets 5 mg
Zyprexa® Tablets 10 mg

< Olanzapine Tablets >

Powerful drug, Designated drug and Prescription-only drug

Storage
The products should be stored at room temperature.

Expiration date
Specified on the outer package or label.

	2.5 mg tablet	5 mg tablet	10 mg tablet
Approval No.	21200AMY00249	21200AMY00250	21200AMY00251
NHI price listing	June 2001	June 2001	June 2001
Date of Marketing	June 2001	June 2001	June 2001

Caution: Use only pursuant to the prescription or directions of a physician, etc.

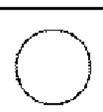
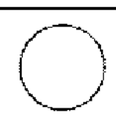
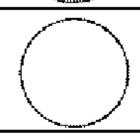
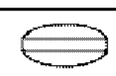
WARNINGS

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 Precautions"**

CONTRAINDICATIONS (This product is contraindicated in the following patients.)

(1) Patients in coma [Coma may be aggravated.]
(2) Patients under strong influence of central nervous system suppressants such as barbiturate derivatives [Central nervous suppression may be enhanced.]
(3) Patients with a history of hypersensitivity to the ingredients of this product
(4) Patients receiving epinephrine [See "Drug interactions"].
(5) Patients with diabetes mellitus and those who have a history of diabetes mellitus

COMPOSITION AND DESCRIPTION**

Brand name		Zyprexa Tablets 2.5mg	Zyprexa Tablets 5mg	Zyprexa Tablets 10mg
Ingredient, Content (olanzapine per one tablet)		2.5 mg	5 mg	10mg
Additives		Lactose, hydroxypropyl cellulose, crospovidon, crystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose 2910, titanium dioxide, macrogol 400, polysorbate 80, carnauba wax		
Color, Dosage form		White film-coated tablet	White film-coated table	White film-coated table
Shape	Front side			
	Reverse side			
	Lateral side			
Size	Diameter	7.1 mm	8.1 mm	10.2 mm
	Thickness	3.4 mm	4.0 mm	5.0 mm
Weight		About 0.14 g	About 0.21 g	About 0.42 g
Identification code		*LILLY* 4112	*LILLY* 4115	*LILLY* 4117

INDICATIONS

Schizophrenia

DOSAGE AND ADMINISTRATION

The usual starting dose of olanzapine for adults is 5 to 10 mg/day orally which may be given once daily.

The routine effective dose is 10 mg/day orally. Dosage should be adjusted appropriately by age and symptoms not to exceed 20 mg/day.

PRECAUTIONS

1. Careful Administration (This product should be administered with care in the following patients.)

(1) Patients with histories of urinary retention, paralytic illeus, narrow angle glaucoma [symptoms may be exacerbated by anticholinergic activity]

(2) Patients with seizure-related conditions such as epilepsy or having a history of such conditions [risk of reducing the seizure threshold]

(3) Patients with liver disorders or patients who are being treated concomitantly with hepatotoxic drugs[can worsen liver disorders]

(4) The elderly [See the section on "Use in the elderly"]

(5) Patients with multiple clearance-decreasing factors (non-smoker, female, elderly) [Plasma concentration of olanzapine may be increased.]

(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) Olanzapine may induce dizziness, tachycardia, orthostatic hypotension, etc. at the beginning of treatment. Olanzapine should be used with caution in patients with cardiovascular disease (history of myocardial infarction or ischemia, heart failure, conduction abnormalies, etc.), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, treatment with antihypertensive medications, etc.).

(5) Since this product has an antiemetic action, it should be noted that any toxic signs associated with other drugs and vomiting induced by ileus and brain tumor may be masked.

(6) Since this product may produce somnolence or decreased attentiveness/concentration/reflex movement etc., patients should be cautioned against working at a high place or engaging in potentially hazardous activities such as operating machinery or driving a motor vehicle.

3. Drug Interactions

A liver drug-metabolizing enzyme CYP1A2 is involved in the metabolism of olanzapine. CYP2D6 is also is considered to be involved in the metabolism. [See "Pharmacokinetics."]

(1) Contraindications for coadministration (This product should not be coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Epinephrine, Bosmin	This product may reverse the action of epinephrine and lower the blood pressure.	Epinephrine stimulates adrenergic alpha- and beta-receptors and its stimulatory effect on beta-receptors becomes prevalent since this product blocks alpha-receptors, resulting in the further lowering of the blood pressure.

(2) Precautions for coadministration (This product should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
CNS suppressants, Barbiturate Derivatives, etc.	Since the inhibition of CNS may be augmented, careful dose adjustments such as dose reduction should be made.	This is attributable to the suppression of CNS caused by this product and CNS suppressants.
Alcohol	Use of alcohol may induce drug interaction and augment the effect.	Alcohol has an inhibitory effect on CNS.
Anticholinergic drugs, Anticholinergic anti-Parkinson agents, Phenothiazines, Tricyclic antidepressants, etc.	Severe anticholinergic toxicities including intestinal paralysis may occur.	This is attributable to anticholinergic effect caused by this drug and anticholinergic drugs.
Dopaminergic agents, Levodopa	The dopaminergic action of these drugs may be attenuated.	This product may antagonize the action of these drugs in the dopaminergic nerve.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Fluvoxamine	Since the plasma concentration of olanzapine is increased, careful dose adjustments such as dose reduction should be made.	These products which have an inhibitory effect on CYP1A2 reduce clearance of olanzapine.
Ciprofloxacin hydrochloride	The plasma concentration of olanzapine may be increased.	These products which have an inhibitory effect on CYP1A2 reduce clearance of olanzapine.
Carbamazepine	The plasma concentration of olanzapine is decreased.	These products which induce CYP1A2 increase clearance of olanzapine.
Omeprazole Rifampicin	The plasma concentration of olanzapine may be decreased.	These products which induce CYP1A2 increase clearance of olanzapine.
Smoking	The plasma concentration of olanzapine is decreased.	Smoking which induces CYP1A2 increase clearance of olanzapine.

4. Adverse Reactions

Of a total of 580 cases studied and included in safety analyses, adverse reactions occurred in 377 cases (65.0%). The major adverse reactions reported included insomnia in 123 cases (21.2%), sleepiness in 97 cases (16.7%), weight increase in 95 cases (16.4%), akathisia in 69 cases (11.9%), tremor in 66 cases (11.4%), malaise in 62 cases (10.7%), anxiety/feeling irritated in 62 cases (10.7%), and excitement/irritability in 58 cases (10.0%). The major abnormalities observed as adverse reactions in laboratory test values present at the end of study participation were ALT elevation (15.8%), prolactin elevation (14.5%), AST elevation (11.5%), trigryceride elevation (10.3%).

(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.

2) **Neuroleptic Malignant Syndrome**: This condition is characterized by symptoms such as akinesia, extreme myotonia, irregular pulse and blood pressure, and sweating, with subsequent fever. If such a sequence of symptoms occurs, discontinue administration and take appropriate measures in addition to general supportive care, including hydration and cooling of the body. Onset of this condition is frequently accompanied by greatly elevated creatinine phosphokinase (CPK) levels and leukocytosis. Impaired renal function accompanied by myoglobinurea has also been noted. There have been reports of persistent fever, with loss of consciousness, dyspnea, circulatory collapse, dehydration, and acute renal failure, leading in some cases to death.

3) **Hepatic function disorder and jaundice:** Hepatic function disorder and jaundice with increase of AST(GOT), ALT(GPT), γ -GTP and Al-P may occur. If case abnormalities are noted, discontinue the administration and take appropriate actions.

4) **Tardive dyskinesia**: Long-term administration of olanzapine may result in the development of involuntary movements, particularly around the mouth, which may persist even after administration is discontinued.

(2) Other adverse reactions

Appropriate measures, such as discontinuing treatment and reducing doses, should be taken if any adverse reactions are observed

Japanese clinical studies and postmarketing reports

Classification	≥ 5%	< 5% and ≥ 1%	< 1%	unknown
Psychoneurological	Insomnia, Somnolence, Headache/headache dull, Dizziness/light-headed feeling	Depressed state, Libido increased, Dizziness on standing up	Seizures, Dysarthria, Unconsciousness, Disinhibition, Feeling strange, Hypesthesia, Memory disturbance, Suicide attempt, Inappropriate laughter, Manic state, Hyperaesthesia, Soliloquy, Twilight state	Anxiety, Feeling irritated, Excitement, Irritability, Hallucination, Numbness, Delusion, Speech disorder
Extra-pyramidal	Akathisia, Tremor, Muscle rigidity,	Salivation, Dystonia, Dyskinesia, Bradykinesia, Gait abnormal	Dysphagia, Eyeballs raise upward, Movements reduced, Restless legs, Rigidity bodily, Tongue movement disturbance	

Classification	≥ 5%	< 5% and ≥ 1%	< 1%	unknown
Cardio-vascular		Blood pressure decreased, Blood pressure increased, Heart pounding, Tachycardia, Hypotension postural	Bradycardia, Extrasystole ventricular, Auricular fibrillation	
Gastro-intestinal	Constipation, Oral dryness	Appetite increased, Anorexia, Nausea, Stomach discomfort, Vomiting, Diarrhoea,	Abdominal pain, Gastric ulcer, Angular stomatitis, Stool black, Hemorrhoidal bleeding, Stools loose	gastritis
Blood		Eosinophilia, Leucopenia, Leukocytosis, Haemoglobin decreased, Haematocrit value decreased	Anaemia, Erythrocytopenia, Polycythaemia, Neutropenia, Neutrophilia, Lymphopenia, Monocytosis, Monocytopenia, Thrombocyto-penia, Thrombocytosis, Eosinopenia	
Endocrine	Prolactin elevation	Menstrual disorder, Prolactin decreased	Lactation, Breast enlargement, Hyperthyroidism	
Hepatic	ALT elevation, AST elevation, Gamma-glutamyl-transferase increased	Phosphatase alkaline increased, LDH increased	Urobilinogen appeared, Total bilirubin increased, Total bilirubin decreased	
Kidney			Albuminuria, Pyelitis, Urinary sedimentation increased, Blood urea nitrogen increased, Blood urea nitrogen decreased, Creatinine blood decreased	Urinary retention, Urinary incontinence
Urinary organs		Micturition disorder	Pollakiuria	
Hyper-sensitivity		Rash	Small papule	Pruritis, facial edema

Classification	≥ 5%	< 5% and ≥ 1%	< 1%	unknown
Metabolic	Triglyceride elevation	Total protein decreased, Cholesterol elevated, Sodium decreased, Chloride decreased, Potassium increased, Sugar urinary	Hyperlipaemia, Diabetes, Water intoxication, Hyperkalaemia, Dehydration, Hypokalaemia, Hyponatraemia, Potassium decreased, Sodium increased, Chloride increased, Triglyceride decreased	Hyperuricaemia
Respiratory		Nasal obstruction		
Others	Weight increase, Malaise, CPK increased	Weakness, Fever, Weight decrease, Diaphoresis, Edema, Albumin decreased, Globulins increased, AG ratio abnormal	Vision blurred, Eye prick pain of Stiffness shoulder, Fracture, Lumbar pain, Chest ache, Death, Hypopyrexia, Hot flushes	

Foreign clinical studies and postmarketing spontaneous reports

Classification	≥ 10%	< 10% and ≥ 1%	< 1% and ≥ 0.1%	Unknown note3)
Psycho-neurological	Gait abnormal note4), Somnolence note2), Hallucination note5)	Dizziness note2)		Seizure
Extra-pyramidal	Parkinsonism note5)	Akathisia note2)		
Cardio-vascular		Hypotension postural note1)	Bradycardia note2)	
Gastrointestinal		Constipation note2), Oral dryness note2), Appetite increased note2)		Pancreatitis
Blood		Eosinophilia note1)		Leucopenia Thrombocyto-penia
Endocrine	Prolactin elevation note1)			
Hepatic		ALT elevation note1), AST elevation note1)		Hepatitis
Hypersensitivity			Photosensitivity reaction note2)	Rash, Angioedema, Pruritis, Urticaria

Classification	≥ 10%	< 10% and ≥ 1%	< 1% and ≥ 0.1%	Unknown note3)
Metabolic		Hyperglycemia notes1, 6), Triglyceride elevation notes1, 7)		Coma diabetic, Diabetic ketoacidosis, Hypertriglyceridemia
Others	Weight increase note1)	Oedema periphera note2) Fatigue note2) Weakness note2)		Priapism, Withdrawal reactions (sweating, nausea, vomiting)

Note
1) As assessed by measured values within the clinical trial database
2) Adverse event identified from the clinical trial database
3) Adverse event identified from postmarketing spontaneous reports
4) Adverse event identified from clinical trials in patients with dementia of the Alzheimer's type.
5) Adverse event identified from clinical trials in parkinsonian patients with the dopamine agonist-induced psychosis.
6) Casual blood glucose: Not less than 160 mg/dL
7) Casual blood triglyceride: Not less than twice the upper limit of fasted blood triglyceride

5. Use in the Elderly

Since physiological functions of elderly people are generally deteriorated and aging is one of the factors that reduce clearance of olanzapine, this drug should be administered carefully.

In elderly patients having other factor(s) associated with reduced clearance of olanzapine (non-smoking status, female, etc.), consideration should be given to initiation of administration at a lower dosage, 2.5 to 5 mg/day, where clinical factors warrant, and monitor the patient's condition. [The clearance of this drug may be decreased in elderly patients having other factor(s) associated with reduced clearance of olanzapine.]

6. Use during Pregnancy, Delivery or Lactation

(1) Since safety during pregnancy has not yet been established, this product should be administered to patients who are pregnant or may become pregnant only if the expected therapeutic benefit is thought to outweigh any possible risk.

(2) Breast feeding should be discontinued when this product is administered to lactating woman. [It has been reported that this product is excreted in the milk of treated human.]

7. Pediatric Use

Safety in children etc. has not been established. [No experience of use.]

8. Overdosage

Signs and symptoms: Very common symptoms reported in olanzapin overdose (≥ 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Other medically significant sequelae of olanzapine overdose include delirium, convulsion, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of 1,500 mg.

Measures to be taken: There is no specific antidote to this product. Induction of emesis is not recommended. In the case of overdose, a gastric lavage should be carried out or activated charcoal should be administered. The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%. Carefully monitoring heart and respiratory functions, etc, hypotension, circulatory collapse and reduced respiratory function should be treated with appropriate measures. Do not use epinephrine, dopamine, or other agents with beta-agonist activity, which may worsen hypotension.

9. Precautions concerning Use

When this product is supplied, a patient should be instructed to take out products from a blister package before administration. [It has been reported that the sharp edges of a blister package swallowed by mistake stick in the esophageal mucosa, cause perforation, and lead to serious complications such as mediastinitis.)

10. Other precautions

(1) During treatment of olanzapine, sudden death with unknown cause was reported.

(2) In carcinogenicity studies, an increase in the incidence of mammary gland tumor was reported in female mice (8 mg/kg/day or more, for 21 months) and female rats (2.5/4 mg/kg/day or more, for 21 months, dose increase on day 211 of administration). These findings are well-known in the rodents as a change related to prolactin level. Neither clinical studies nor epidemiologic studies have shown a clear association between chronic treatment of this drug and this class of drugs and tumorigenesis in humans.

Zyprexa MDL 1596: Confidential-Subject to Protective Order
ZY200391035

PHARMACOKINETICS

1. Absorption, plasma concentration

Olanzapine was administered to healthy volunteers at a 5 mg single oral dose (fasting) [1].

Dose	Tmax (hr)	Cmax (ng/mL)	$t_{1/2}$ (hr)	AUC_{0-96} (ng・hr/mL)
5mg× 1 tablet	4.8±1.2	10.5±2.2	28.5±6.1	279±86.6

The absorption is not affected by food.

According to the population pharmacokinatic analysis (113 Japanese patients, 415 blood samples from steady state, analyzed by NONMEM version V Level 1) based on the assumption that the same Ka and Vdss/F values are set to all population, there might be small difference in reference value of the clearance by the smoking status and gender. The population reference values of the clearance and 95% confidence limit are, 14.3 L/hr (11.8-16.8) in male smoker, and 11.0 L/hr (9.0-13.0) in female nonsmoker. However, decrease of clearance by aging was not observed in each subpopulation.

(foreign data)

Plasma concentrations of olanzapine showed dose protional in trials studying doses from 2.5 to 20 mg in patients. It was confirmed that pharmacokinetics of olanzapine is linear. The mean terminal elimination half-life was 33 hours (20.7-54.1 hours, 5-95 percentile) and the mean plasma clearance was 26.1 L/hr. (12-47 L/hr., 5-95 percentile) in healthy volunteers. Steady state concentrations are reached within one week administration.

2. Protein binding

About 93% (in vitro, ultra-centrifugation method). Olanzapine is bound predominantly to albumin and alpha-1-acid-glycoprotein.

3. Metabolites and pathway

The enzymes responsible for metabolism are glucuronyltransferases, flavin containing monooxygenase and cytochrome P450. The 10-N-glucuronide and 4'-N-glucuronide metabolites of olanzapine are formed by direct glucuronidation [2]. Olanzapine 10-N-glucuronide is the major metabolite in both the plasma and the urine. The formation of the 4'-N-oxide metabolite has been correlated with flavin containing monooxygenase. The formation of the predominant oxidative metabolite 4'-N-demethyl olanzapine is mediated by cytochrome P450 isoform CYP1A2. The formation of the relatively minor metabolite 2-hydroxymethyl olanzapine is mediated by CYP2D6. Both the 4'-N-desmethyl and 2-hydromethyl metabolites exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine. Cytochrome P450 isoform CYP2D6 status does not significantly affect the overall clearance of olanzapine.

The steady state plasma concentration ratio of olanzapine to olanzapine 10-N-glucuronide to 4'-N-desmethyl olanzapine is 100:44:31

4. Drug interactions

Since fluvoxamine is thought to inhibit CYP1A2, the plasma concentration was increased by the concomitant use with fluvoxamine. The effect in male (all smokers) was greater than in females (all nonsmokers). Cmax was increased by 75% in males (smokers) and by 52% in females (nonsmokers). AUC_{0-24} was increased by 108% in males (smokers) and by 52% in females (nonsmokers). Clearance (CLp/F) was decreased by 52% in males (smokers) and by 37% in females (nonsmokers).

Since carbamazepine is thought to induce CYP1A2, the plasma olanzapine concentration was decreased by the concomitant use with carbamazepine, with a 24% decrease in Cmax, and a 34% decrease in $AUC_{0-\infty}$. The plasma olanzapine concentration was slightly increased by the concomitant use with fluoxetine (not approved in Japan). Cmax was increased by 16% and Clearance (CLp/F) was decreased by 16%. This change was considered attributable to fluoxetine's inhibitory effect on CYP2D6.

The typical value for the clearance of olanzapine in smokers in approximately 35% higher than for nonsmokers because smoking is known to induce CYP1A2.

5. Excretion route and rate (foreign data)

Approximately 57% and 30% of radioactivity associated with an oral dose of radiolabeled olanzapine to healthy volunteers are excreted in urine and feces, respectively for 21 days.

6. Others (foreign data)

Renal dysfunction: Ten renal dysfunction subjects showed no significant difference in the pharmacokinetics of olanzapine.

Hepatic dysfunction: Although hepatic dysfunction might be expected to reduce the clearance of olanzapine, eight hepatic dysfunction subjects showed no significant difference in the pharmacokinetics of olanzapine.

Elderly: In single-dose study, sixteen subjects, over 65 years, showed a 53% longer half life compared to non-elderly (52 hours versus 34 hours). In multiple-dose (14 days) study, eight subjects, over 65 years, showed the half life of 59 hours.

Gender/smoking: Clearance of olanzapine is approximately 30% lower in women than in men, and 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended. In case of the combination with gender and smoking status, average clearance values are the highest in male smokers followed by female smokers, male nonsmokers, and lowest in female nonsmokers.

CLINICAL STUDIES

The main results of clinical trials conducted in Japan in a total of 567 olanzapine-treated patients in efficacy analysis including the double-blind, controlled study are as follows;

1. **Open-label clinical studies**
   The efficacy rate of moderately improved or better in total 81 patients with schizophrenia, treated for up to 8 weeks, in the first open-label study was 59.3% (48/81) [3]. In a second 8 week open-label study with total 156 schizophrenic patients, the efficacy rate as moderately improved or better was 58.3% (91/156) [4].

2. **Double-blind, controlled clinical study**
   In a double-blind, controlled clinical study [5], 44.4% (40/90) of olanzapine-treated patients showed moderate improvement or better, that indicated the usefulness of this drug against schizophrenia.

3. **Foreign double-blind controlled clinical study analyses**
   In a double-blind controlled clinical study using haloperidol (15+/-2.5mg/day), placebo, and olanzapine fix dosed (low dose: 5+/-2.5mg/day, middle dose: 10+/-2.5mg/day, high dose: 15+/-2.5mg/day), the middle and high dose arms of olanzapine showed significantly greater improvement in psychiatric symptoms including both positive and negative symptoms to placebo arm. The high dose arm of olanzapine showed significantly greater improvement in negative symptoms. All of olanzapine treatment arms showed significantly improvement of extrapyramidal symptoms (EPS) but EPS worsened during haloperidol treatment. All of olanzapine treatment arms showed significantly less development of parkinsonism and akathisia [6].
   In analyses of 3 large double-blind, long-term extension studies for patients showing good acute improvement with either olanzapine or haloperidol treatment, olanzapine was more effective than haloperidol in maintaining the good acute response and preventing relapse of schizophrenia [7].
   In analyses of the development of tardive dyskinesia during double-blind, long-term extension treatment with either olanzapine or haloperidol, the rate of development during olanzapine treatment was less than $1/10^{th}$ the rate of development of tardive dyskinesia during haloperidol treatment. The difference between treatments was significant [8].

EFFICACY PHARMACOLOGY

Olanzapine is an atypical antipsychotic that is structurally a thienobenzodiazepine distinct structurally from any other available antipsycotics. Preclinical pharmacology studies have shown its pharmacological properties to be different from those of typical antipsychotics.

1. **Pharmacological effects**
   (1) Selective activities in animal models for symptoms of schizophrenia
   Olanzapine is effective in animal models for schizophrenia including the conditioned avoidance response [9] (an indicator of positive symptoms), disruption of prepulse inhibition [10] (an indicator of negative symptoms and cognitive impairment), social withdrawal [11] (an indicator of negative symptoms), conflict [9,12] (an indicator of negative symptoms and anxiety), forced swimming (an indicator of depressive symptoms), etc. at lower doses than that producing catalepsy [9] (an indicator of EPS).
   (2) Selectivity for the mesolimbic system and prefrontal cortex
   Olanzapine shows selectivity for the mesolimbic system and prefrontal cortex that are associated with antipyschotic activities of drugs compared with nigrostriatal system that is thought to mediate EPS in electrophysiological [13] and histological studies [14].
   (3) Preferential interactions with unbalanced neuronal transmissions in schizophrenia
   The hypoactive dopaminergic D_1 transmission in the prefrontal cortex and disrupted glutamate systems are hypothesized to be involved in schizophrenia. Olanzapine increases dopamine and norepinephrine release in prefrontal cortex [15] and restores disrupted glutamatergic transmission [10,11].

2. **Mechanism of action:**
   Olanzapine has the multiple receptor interaction that are thought to be responsible for it novel efficacy for positive, negative symptoms, cognitive impairment, anxiety, depressive symptoms and minimal induction of EPS (multi-acting), and it's multiple receptor interaction is thought to be responsible for the selective action for the brain regions (receptor-targeting) [16-18]. It shows high affinity in the same concentration range for a number of receptors including dopamine D_2-type (D_2, D_3, D_4), 5-$HT_{2A, 2B, 2C}$, 5-HT_6, α_1-adrenergic and histamine H_1 as well as lower affinity for dopamine D_1-type (D_1, D_5) and 5-HT_3 receptors [19,20]. The affinity of olanzapine for muscarinic receptor subtypes (M_1, M_2, M_3, M_4, M_5) is weaker *in vivo* than that *in vitro* [21]. This drug is an antagonist for these receptors [22]. Moreover, the increased dopamine and norepinephrine release in prefrontal cortex [15] and restoration of disrupted glutaminergic transmissions [10,11] by olanzapine may be also due to the multiple receptor interactions [17].

PHYSICOCHEMICAL PROPERTIES OF THE ACTIVE INGREDIENT

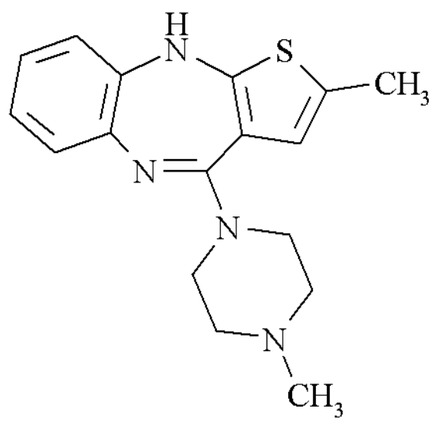
Nonproprietary name: Olanzapine (JAN)

Chemical name:

2-methyl-4-(4-methylpiperazin-1-yl)-10H-thieno[2,3-b][1,5]benzodiazepine

Molecular formula: $C_{17}H_{20}N_4S$

Molecular weight: 312.44
Structural formula:



Description:
A yellow crystalline powder.
It is slightly soluble in ethanol (99.5%), very slightly soluble in methanol, and practically insoluble in water.
Melting point: about 195°C (decomposition)
Partition coefficient: 1.8 (pH 5, buffer/octanol)

PACKAGING

2.5 mg tablets:
100 tablets in press-through packages (10 tablets × 10), 100 tablets, 1000 tablets
5 mg tablets:
100 tablets in press-through packages (10 tablets × 10), 100 tablets, 1000 tablets
10 mg tablets:
100 tablets in press-through packages (10 tablets × 10), 100 tablets, 1000 tablets

REFERENCES

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