OLANZAPINE (Systemic)

Category

Antipsychotic.

Indications

Accepted

Psychotic disorders (treatment)¾Olanzapine is used to treat the manifestations of psychotic disorders 1.

The effectiveness of olanzapine therapy for more than 6 weeks has not been evaluated in controlled trials 1.

Other actions/effects:

A modest elevation in prolactin levels persists during chronic olanzapine administration 1 , probably due to antagonism of dopamine D 2 receptors 1.

The clinical significance of elevated prolactin levels is unknown for most patients 1 , although such effects as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating medications 1.

Also, studies have found approximately one third of human breast cancers to be prolactin-dependent in vitro .

Precautions to Consider

Carcinogenicity/Tumorigenicity

In carcinogenicity studies, significant increases in the incidence of mammary gland adenomas and adenocarcinomas occurred in female mice receiving 0.5 times the maximum recommended human daily dose (MRHD) of 20 mg per day 2 of olanzapine on a mg per square meter of body surface area (mg/m 2) basis 1 and in female rats receiving two times the MRHD of olanzapine on a mg/m 2 basis 1.

A toxicity study in rats showed prolactin levels to be elevated up to fourfold at the same doses of olanzapine that were used in the carcinogenicity studies 1.

The increased incidence of mammary gland neoplasms found in rodents after chronic administration of antipsychotic drugs is considered to be prolactin mediated 1.

Drugs that antagonize dopamine D 2 receptors, including olanzapine, are associated with increased prolactin levels in humans 1.

Because studies have found approximately one third of human breast cancers to be prolactin-dependent in vitro1 , this prolactin level elevation may be of importance when considering use of these medications in patients with previously detected breast cancers 1.

However, there has been no association shown between chronic administration of medications that elevate prolactin levels and tumorigenesis in either epidemiological or clinical studies to date 1.

Current evidence is too limited to be conclusive 1.

Two carcinogenicity studies were conducted in which mice received olanzapine for 78 weeks at doses ranging from 0.06 to 5 times the MRHD on a mg/m 2 basis (0.8 to 5 times the MRHD in one study, and 0.06 to 2 times the MRHD in the other study) 1.

In one of these studies, a significant increase in the incidence of liver hemangiomas and hemangiosarcomas was seen in female mice dosed at two times the MRHD 1.

In the other study, this increased incidence of liver hemangiomas and hemangiosarcomas was not seen, but early mortality was increased in male mice receiving five times the MRHD 1.

Mutagenicity

Olanzapine demonstrated no mutagenic potential in the following tests: Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters 1.

Pregnancy/Reproduction

Fertility¾The mating performance, but not the fertility, of male rats was impaired during administration of olanzapine at doses that were 11 times the maximum recommended human daily dose (MRHD) of 20 mg per day 2 on a mg per square meter of body surface area (mg/m 2) basis 1.

The impairment of mating performance was reversed with discontinuation of olanzapine administration 1.

Studies in female rats indicate that olanzapine may produce a delay in ovulation 1.

When olanzapine was administered at doses that were 1.5 times the MRHD on a mg/m 2 basis, female rats showed a decrease in fertility 1.

At doses that were 2.5 times the MRHD on a mg/m 2 basis, female rats showed an increased precoital period, and a reduced mating index 1.

Pregnancy¾Adequate and well-controlled studies in humans have not been done 1.

Of seven pregnancies that occurred during clinical trials with olanzapine, two resulted in normal births, one resulted in neonatal death due to a cardiovascular defect, three ended in therapeutic abortions, and one ended in spontaneous abortion 1.

Olanzapine crosses the placenta in rats 1.

No evidence of teratogenicity was seen in rats administered olanzapine at doses up to nine times the MRHD on a mg/m 2 basis 1 , or in rabbits administered olanzapine at doses up to 30 times the MRHD on a mg/m 2 basis 1.

At the maximum doses in these studies, early fetal resorptions and increased numbers of nonviable fetuses were observed in rats 1 , and increased fetal resorptions and decreased fetal weight were observed in rabbits 1.

The maximum dose used in the rabbit study was considered to be maternally toxic 1.

Also, in rats, gestation was prolonged at a dose that was five times the MRHD on a mg/m 2 basis 1.

FDA Pregnancy Category C 1.

Labor and delivery¾The effect of olanzapine on labor and delivery in humans is unknown 1.

Olanzapine did not affect parturition in rats 1.

Breast-feeding

It is not known whether olanzapine is distributed into human breast milk 1.

However, olanzapine is distributed into the milk of rats 1 , and use in nursing mothers is not recommended 1.

Pediatrics

No information is available on the relationship of age to the effects of olanzapine in pediatric patients. Safety and efficacy have not been established in patients up to 18 years of age 1.

Geriatrics

No geriatrics-specific problems that would limit the usefulness of olanzapine in the elderly were seen in studies that included elderly subjects 1.

However, the mean elimination half-life was found to be about 1.5 times greater in elderly subjects than in younger subjects in one study 1.

Pharmacogenetics

Olanzapine clearance is approximately 30% lower in females than in males 1.

However, no differences in adverse effects or efficacy were seen in clinical studies 1 , and dosage adjustments based on gender are not recommended 1.

Comparisons of pharmacokinetic data from studies conducted in Japan with data from studies conducted in the U.S. indicate a twofold higher exposure to olanzapine in Japanese subjects when doses are equivalent 1.

However, no clinically significant differences in safety or efficacy were seen when comparisons were made among Caucasian, African-descent, and pooled Asian and Hispanic patient groups 1.

Dosage adjustments based on race are not recommended 1.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: In vitro studies indicate that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A 1.

Therefore, olanzapine is not expected to interfere with the metabolism of medications that are metabolized by these enzymes 1.

Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Agents that induce CYP1A2 1 or glucuronyl transferase enzymes 1 , such as carbamazepine 1 , omeprazole 1 , or rifampin 1

(olanzapine clearance may be increased 1 ; carbamazepine therapy at a dose of 200 mg two times a day increased olanzapine clearance by about 50% 1)

Agents that inhibit CYP1A2 1 , such as fluvoxamine 1

(olanzapine clearance may be decreased 1 , although, because multiple enzymes are involved in olanzapine metabolism, the effect of inhibiting one isozyme may not be significant 1)

>> Alcohol 1 or

>> Central nervous system (CNS) depression-producing medications, other 1 (See Appendix II)

(additive CNS depressant effects may occur 1 ; orthostatic hypotension may be potentiated 1)

>> Anticholinergics, other 1 (See Appendix II)

(anticholinergic effects of either these medications or olanzapine may be increased 1 ; disruption of the body's ability to reduce core temperature may be a special consideration 1)

Antihypertensive agents 1

(hypotensive effects of these medications or olanzapine may be enhanced 1)

Dopamine agonists 1 or

Levodopa 1

(effects of these medications may be antagonized by olanzapine 1)

>> Hepatotoxic medications 1 (See Appendix II)

(asymptomatic but clinically significant alanine aminotransferase [ALT (SGPT)] value increases occurred in about 2% of patients in premarketing studies of olanzapine 1 ; about 1% of patients discontinued olanzapine treatment due to increased transaminase levels 1 ; caution is recommended when olanzapine is used concurrently with hepatotoxic medications 1)

Smoking, cigarette 1

(olanzapine clearance is increased by about 40% 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) 1 values and

Aspartate transaminase (AST [SGOT]) 1 values and

Gamma-glutamyl transpeptidase (GGT) 1 values

(in premarketing studies, about 2% of patients with baseline ALT [SGPT] values £ 90 international units per L [IU/L] had ALT value increases to > 200 IU/L 1 during treatment with olanzapine; none of these patients experienced symptoms of liver function impairment 1 , and in most the ALT value returned to normal with continued olanzapine treatment 1 ; asymptomatic increases in AST and GGT were seen also 1 ; about 1% of patients in clinical trials discontinued olanzapine treatment due to increased transaminase values 1)

Prolactin concentration 1 , serum

(sustained elevations occur during olanzapine therapy 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists

>> Hypersensitivity to olanzapine 1

Risk-benefit should be considered when the following medical problems exist

>> Alzheimer's dementia 1

(dysphagia associated with olanzapine use may increase risk of aspiration pneumonia 1 ; possible increased risk of seizures because of lowered seizure threshold with Alzheimer's dementia 1)

>> Breast cancer 1 , or history of

(prolactin-dependent breast cancers may be exacerbated)

>> Cardiovascular disease 1 , including:
Conduction abnormalities 1 or
Heart failure 1 or
Myocardial infarction or ischemia, or history of, 1 or

>> Cerebrovascular disease 1 or

>> Conditions that would predispose to hypotension 1 , including:
Dehydration 1 or
Hypovolemia 1

(orthostatic hypotension may be exacerbated 1 , or may exacerbate preexisting cardiovascular or cerebrovascular conditions 1)
(dehydration may predispose to increased core body temperature 1 , and antipsychotic medications may disrupt the body's ability to lower core body temperature 1 , thus increasing the risk of heatstroke)

Drug abuse or dependence 1 , history of

(patients should be observed closely for signs of misuse or abuse of olanzapine, as with any new CNS medication 1)

>> Glaucoma, narrow angle 1 or

>> Paralytic ileus, history of 1 or

>> Prostatic hypertrophy, clinically significant 1

(may be exacerbated due to cholinergic antagonism by olanzapine 1)

>> Hepatic function impairment 1

(in premarketing studies, about 1% of patients discontinued olanzapine treatment due to increased transaminase levels 1 ; transaminase levels should be assessed periodically in patients with significant hepatic disease 1)

Seizures, or history of 1

(seizures occurred rarely in premarketing studies of olanzapine 1 ; it is recommended that olanzapine be used with caution in patients with a history of seizures or a decreased seizure threshold 1)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Alanine aminotransferase (ALT [SGPT]) values 1 and

Aspartate transaminase (AST [SGOT]) values 1

(recommended periodically in patients with significant hepatic disease 1)

Careful supervision of patients with suicidal tendencies 1

(recommended in high-risk patients, since the possibility of a suicide attempt is inherent in schizophrenia 1)

Side/Adverse Effects

Note: Disturbances of body temperature regulation have been associated with use of other antipsychotic agents 1.

Caution is advised in administering olanzapine to patients who will be experiencing conditions that may contribute to an elevation in core body temperature 1 , such as strenuous exercise 1 , exposure to extreme heat 1 , or dehydration 1.

The neuroleptic malignant syndrome (NMS) has been associated with the use of other antipsychotic agents 1.

NMS is a potentially fatal symptom complex that may include hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability seen as irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrythmia 1.

Elevated creatine kinase, myoglobinuria (rhabdomyolysis), and acute renal failure also may occur 1.

Differential diagnosis should exclude serious medical illnesses, such as pneumonia or systemic infection presenting in conjunction with extrapyramidal effects, as well as central anticholinergic toxicity, heatstroke, drug fever, and primary CNS pathology 1.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Agitation 1; akathesia 1 (restlessness or need to keep moving); extrapyramidal effects, parkinsonian 1 (difficulty in speaking or swallowing; stiffness of arms or legs; trembling or shaking of hands and fingers); personality disorder 1 (nonaggressive objectionable behavior 1)

Note: Akathesia and extrapyramidal effects are dose-related 1.

Incidence less frequent

Chest pain 1; extrapyramidal effects, dystonic 1 (inability to move eyes; muscle spasms of face, neck, and back; twitching movements); fever 1; flu-like symptoms 1; mood or mental changes, including amnesia 1; anxiety 1; euphoria 1; hostility 1; and nervousness 1; peripheral edema 1 (swelling of feet or ankles); tardive dyskinesia 1 (lip smacking or puckering; puffing of cheeks; rapid or worm-like movements of tongue; uncontrolled chewing movements; uncontrolled movements of arms and legs)

Note: Tardive dyskinesia occurs more frequently in elderly patients, especially elderly women 1.

The risk of developing the syndrome, and of experiencing irreversible effects, appears to increase with treatment duration and total cumulative dose 1 , although it may develop at any time during antipsychotic therapy 1.

There is no known treatment for tardive dyskinesia 1 , although partial or complete remission may occur when the antipsychotic medication is withdrawn 1.

Alternatively, the antipsychotic medication may suppress the signs of the syndrome 1 , masking the underlying process 1.

For these reasons, olanzapine should be used only in those patients with chronic illness that is responsive to antipsychotic medication 1 , and for whom potentially less harmful treatments are unavailable or inappropriate 1.

Also, the smallest effective dose of olanzapine should be used and the need for continuing treatment should be assessed periodically 1.

Incidence rare

Dyspnea 1 (trouble in breathing); facial edema 1 (swelling of face); menstrual changes 1; skin rash 1; water intoxication 1 (confusion; mental or physical sluggishness)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Amblyopia 1 (problems with vision); asthenia 1 (weakness); constipation 1; dizziness 1; drowsiness 1; dry mouth 1; headache 1; increased weight 1; postural hypotension 1 (dizziness or fainting when getting up suddenly from a lying or sitting position); rhinitis 1 (runny nose); tremor 1 (trembling or shaking)

Note: Asthenia, drowsiness, dry mouth, and tremor are dose-related 1.

Postural hypotension is most likely to occur during the initial dose-titration period 1.

During premarketing long-term continuation treatment with olanzapine (median exposure 238 days), 56% of patients had weight gain > 7% of their baseline weight 1.

The average weight gain was 5.4 kg 1.

Incidence less frequent

Abdominal pain 1; articulation impairment 1 (speaking unclearly); hypertonia 1 (tightness of muscles); hypotension 1 (low blood pressure); increased appetite 1; increased cough 1; increased salivation 1 (watering of mouth); insomnia 1 (trouble in sleeping); joint pain 1; nausea 1; pharyngitis 1 (sore throat); stuttering 1; tachycardia 1 (fast heartbeat); thirst 1; urinary incontinence 1 (trouble in controlling urine); vomiting 1; weight loss 1

Note: Nausea is dose related 1.

Incidence rare

Decreased libido 1 (decrease in sexual desire); diplopia 1 (double vision); palpitation 1 (awareness of heartbeat); photosensitivity 1 (increased sensitivity of skin to sunlight)

Overdose

For specific information on the agents used in the management of olanzapine overdose, see:
· Charcoal, Activated (Oral-Local) monograph; and
· Sympathomimetic Agents¾Cardiovascular Use (Parenteral-Systemic) monograph.
For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Acute

Note: During premarketing trials, 67 cases of acute overdosage with olanzapine were identified 1.

The highest reported ingestion was 300 mg 1.

The only symptoms reported in this patient were drowsiness and slurred speech 1.

Among overdose patients who were evaluated in hospitals, none showed changes in laboratory analyses or electrocardiograms (ECG), and vital signs were usually within normal limits 1.

Treatment of overdose

Multiple drug involvement should be considered 1.

There is no specific antidote to olanzapine 1.

To decrease absorption¾Gastric lavage, after intubation if patient is unconscious, and administration of activated charcoal with a laxative should be considered 1.

Activated charcoal has been shown to reduce absorption of olanzapine 1 , and may be of use since olanzapine does not reach peak plasma levels for approximately 6 hours following ingestion 1.

The risk of aspiration with induction of emesis may be increased by possible obtundation, seizures, or dystonic reaction of the head and neck 1.

Specific treatment¾Hypotension and circulatory collapse may be treated with intravenous fluids and/or sympathomimetic agents 1.

Because of olanzapine-induced alpha blockade, sympathomimetics with beta agonist activity, such as epinephrine and dopamine, may worsen hypotension and should not be used 1.

Monitoring¾Continuous ECG monitoring should be employed to detect possible arrhythmias 1.

Close medical supervision should continue until patient recovers 1.

Supportive care¾Airway should be established and maintained to ensure adequate oxygenation and ventilation 1.

Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Note: Olanzapine is not removed by dialysis 1.

Patient Consultation

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance)
Before using this medication

>> Conditions affecting use, especially:

Carcinogenicity/Tumorigenicity

Increase in mammary gland neoplasias seen in animal studies; sustained prolactin level elevations with olanzapine use; one third of human breast cancers are prolactin-dependent in vitro ; no association between chronic administration of prolactin level-increasing antipsychotic medications and tumorigenesis seen in epidemiological or clinical studies in humans; evidence inconclusive
Pregnancy¾Seven pregnancies occurring during clinical trials ended in two normal births, one neonatal death due to cardiovascular defect, one spontaneous abortion, three therapeutic abortions
Breast-feeding¾Distributed into the milk of rats; use in nursing mothers not recommended
Dental¾Possible dryness of mouth

Other medications, especially alcohol, anticholinergics, CNS depression-producing medications, or hepatotoxic medications
Other medical problems, especially hypersensitivity to olanzapine, Alzheimer's dementia, breast cancer, cardiovascular disease, cerebrovascular disease, conditions that would predispose to hypotension, glaucoma, hepatic function impairment, paralytic ileus, or prostatic hypertrophy
Proper use of this medication

Compliance with therapy; not taking more or less medicine than prescribed

Taking with or without food, on a full or empty stomach, as directed by physician

>> Proper dosing
>> Proper storage
Precautions while using this medication

Possible drowsiness, impaired judgement, thinking, motor skills, or vision; caution when driving, operating machinery, or doing jobs requiring alertness, coordination, or clear vision

Possible orthostatic hypotension; rising slowly from a sitting or lying position

Possible impairment of ability to regulate core body temperature; avoiding overheating and dehydration

Avoiding use of alcoholic beverages; not taking other CNS depressants unless prescribed by physician

Side/adverse effects

Signs of potential side effects, especially agitation, akathesia, extrapyramidal effects, personality disorder, chest pain, fever, flu-like symptoms, mood or mental changes, peripheral edema, tardive dyskinesia, dyspnea, facial edema, menstrual changes, skin rash, and water intoxication

General Dosing Information

Since the possibility of suicide is inherent in schizophrenia, patients should not have access to large quantities of olanzapine 1.

To reduce the risk of overdose, the patient should be supplied with the smallest quantity of medication necessary for satisfactory patient management.

Diet/Nutrition

Olanzapine may be taken without regard to food 1.

For treatment of adverse effects

Neuroleptic malignant syndrome (NMS)¾Recommended treatment consists of the following:
· Discontinuing olanzapine and other drugs not essential to current therapy1.

· Providing intensive symptomatic treatment and medical monitoring 1.

· Treating any concomitant serious medical problems for which specific treatments are available 1.

· After recovery, giving careful consideration to the reintroduction of antipsychotic drug therapy in patients with severe psychosis requiring treatment, because of possible recurrence of NMS 1 ; closely monitoring patients in whom antipsychotic drug therapy is reintroduced after recovery from NMS 1.

Tardive dyskinesia¾There is no known effective treatment 1.

If signs and symptoms of tardive dyskinesia appear, discontinuation of olanzapine treatment should be considered if clinically feasible 1.

To minimize the occurrence of tardive dyskinesia, chronic antipsychotic treatment should be in the smallest effective dose for the shortest duration necessary to produce a satisfactory clinical response 1.

Oral Dosage Forms

OLANZAPINE TABLETS

Usual adult dose

Antipsychotic¾
Oral, initially 5 to 10 mg once a day 1 , with a target dose of 10 mg once a day within several days 1.

Dosage may then be adjusted as needed and tolerated at increments or decrements of 5 mg a day 1 , at intervals of not less than one week 1.

Note: The risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg a day 1.

If hypotension occurs, a more gradual titration to the target dose may be considered 1.

While individual factors that decrease olanzapine clearance do not necessitate dosage reduction 1 , patients exhibiting a combination of these factors, such as an elderly female nonsmoker, should begin therapy with an initial dosage of 5 mg a day 1.

Dosage should be increased cautiously in these patients if clinically necessary 1.

Debilitated patients 1 , patients predisposed to hypotensive reactions 1 , and patients who may be more pharmacodynamically sensitive to olanzapine 1 should begin therapy with an initial dosage of 5 mg a day 1.

Dosage should be increased cautiously in these patients if clinically necessary 1.

In clinical trials, dosages above 10 mg a day were not shown to be more efficacious than 10 mg a day 1.

Usual adult prescribing limits

20 mg a day 1, 2.

Usual pediatric dose

Antipsychotic¾
Safety and efficacy in children up to 18 years of age have not been established 1.

Usual geriatric dose

Antipsychotic¾
See Usual adult dose1, 2.

Usual geriatric prescribing limits

See Usual adult prescribing limits2.

Strength(s) usually available

U.S.¾5 mg (Rx)[Zyprexa (carnauba wax) (color mixture white) (crospovidone) (FD&C Blue No. 2 Aluminum Lake) (hydroxypropyl cellulose) (hydroxypropyl methylcellulose) (lactose) (magnesium stearate) (microcrystalline cellulose) 1]

7.5 mg (Rx)[Zyprexa (carnauba wax) (color mixture white) (crospovidone) (FD&C Blue No. 2 Aluminum Lake) (hydroxypropyl cellulose) (hydroxypropyl methylcellulose) (lactose) (magnesium stearate) (microcrystalline cellulose) 1]

10 mg (Rx)[Zyprexa (carnauba wax) (color mixture white) (crospovidone) (FD&C Blue No. 2 Aluminum Lake) (hydroxypropyl cellulose) (hydroxypropyl methylcellulose) (lactose) (magnesium stearate) (microcrystalline cellulose) 1]

Packaging and storage:

Store between 20 and 25 °C (68 and 77 °F) 1 , unless otherwise specified by manufacturer. Protect from light and moisture 1.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause dizziness or drowsiness.

References

1 Zyprexa package insert (Eli Lilly¾US), Rev 9/96, Rec 10/96.

2 Personal communication, Medical Information Department, Eli Lilly and Company, 10/25/96.

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