OLANZAPINE
SALVEO®
10 mg FILM-COATED TABLET
ANTIPSYCHOTIC

FORMULATION
Each film-coated tablet contains:
Olanzapine.. 10 mg

PRODUCT DESCRIPTIONS
Olanzapine (Salveo) 10 mg is a white, capsule-shaped, film-coated tablet.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Olanzapine is an atypical antipsychotic,antimanic and mood stabilizing agent that shows a broad pharmacologic profile across a number of receptor systems.

Olanzapine's mechanism of action, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that its efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. Olanzapine's mechanism of action in the treatment of acute manic or mixed episodes associated with bipolar I disorder is unknown.

Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$, dopamine D_{1-4}, histamine H_1, and adrenergic α_1 receptors. Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ and muscarinic M_{1-5}. Olanzapine binds weakly to $GABA_A$, benzodiazepine and ß-adrenergic receptors.

Antagonism at receptors other than dopamine and $5HT_2$ may explain some of olanzapine's other therapeutic and side effects. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic-like effects; antagonism of histamine H_1 receptors may explain somnolence and antagonism of adrenergic α_1 receptors may explain orthostatic hypotension observed with this drug.

Pharmacokinetics
Olanzapine is well absorbed after oral administration. Peak plasma concentration is reached in approximately 6 hours after an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Olanzapine displays linear kinetics over the clinical dose range of 1 to 20 mg. Food does not affect the rate or extent of olanzapine absorption.

The half-life of olanzapine ranges from 21 to 54 hours. Administration of olanzapine once daily leads to steady-state concentrations in about one week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life and clearance of olanzapine may vary between individuals on the basis of smoking status, gender and age.

Olanzapine is extensively distributed throughout the body. Its volume of distribution is approximately 1,000 L. The drug is highly protein-bound (93%) over the concentration range of 7 to 1,110 ng/mL, binding primarily to albumin and α_1-acid glycoprotein. Olanzapine and its glucuronide metabolite have been shown to cross the placenta in humans. It is also distributed into milk.

Olanzapine is metabolized in the liver primarily by direct glucuronidation and cytochrome P450 (CYP)-mediated oxidation. It is highly metabolized, with 7% of the dose recovered in the urine as unchanged drug. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. The major circulating metabolite is the 10-N-glucuronide, which is pharmacologically inactive and does not pass the blood brain barrier. Cytochromes P450 CYP1A2 and P450 CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites; both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent, olanzapine.

Olanzapine's mean terminal elimination half-life is 33 hours (21 to 54 hours) and the mean olanzapine plasma clearance is 26 L/hr (12 to 47 L/hr).

Special Populations:
Renal Impairment: Renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine since olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based on the degree of renal impairment is not required. Olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment: While the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects with clinical significant (Childs Pugh Classification A and B) cirrhosis showed little effect on the pharmacokinetics of olanzapine.

Geriatric: In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (≥65 years old) than in non elderly subjects (<65 years old). Caution should be exercised in dosing the elderly, particularly if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.

Gender: Olanzapine's clearance is approximately 30% lower in women than in men. However, there are no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender is not needed.

Smoking: Clearance of olanzapine is about 40% higher in smokers than in nonsmokers. However, dosage modifications are not recommended.

Combined Effects: The combined effects of age, smoking and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males may be 3 times higher than that in elderly nonsmoking females. Dosing adjustment may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine.

INDICATIONS
- **Schizophrenia**
  - Acute and maintenance treatment of schizophrenia and related psychoses in adults and adolescents (13 to 17 years old)
- **Bipolar I Disorder (Manic or Mixed Episodes)**
  - As monotherapy for the acute and maintenance treatment of manic or mixed episodes associated with Bipolar I Disorder in adults and adolescents (13 to 17 years old)
  - Adjunct to valproate or lithium in the treatment of manic or mixed episodes associated with Bipolar I Disorder in adults
  - For preventing recurrence of manic, mixed or depressive episodes in Bipolar I Disorder
- **In Combination with Fluoxetine:**
  - Acute treatment of depressive episodes associated with Bipolar I Disorder in adults and children (10 to 17 years old)
    Olanzapine monotherapy is not indicated for the treatment of depressive episodes associated with Bipolar I Disorder
  - Acute treatment of treatment-resistant depression in adults (major depressive disorder in patients who do not respond to two separate trials of different antidepressants of adequate dose and duration in the current episode)
    Olanzapine monotherapy is not indicated for the treatment of treatment-resistant depression

DOSAGE AND ADMINISTRATION
Olanzapine alone or in combination with fluoxetine is administered orally once a day, with or without food.

Schizophrenia

Usual Recommended Olanzapine Oral Dose	
INITIAL TREATMENT	
Adults (≥ 18 years old)	**Adolescents (13 to 17 years old)**
Recommended Starting Dose: 5 to 10 mg/day, with a target dose of 10 mg/day within several days. Further dosage adjustment, if indicated, should generally occur at intervals of not less than one week, since steady state for olanzapine would not be achieved for approximately one week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg/day are recommended.	**Recommended starting dose:** 2.5 or 5 mg, with a target dose of 10 mg/day. When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended. The safety and efficacy of doses above 20 mg/day have not been evaluated in clinical trials.
MAINTENANCE TREATMENT The optimum duration of olanzapine therapy is currently unknown. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.	
The efficacy of olanzapine, 10 to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on olanzapine for approximately 8 weeks and were then followed for relapse has been shown in a placebo-controlled trial.	The efficacy of olanzapine for the maintenance treatment of schizophrenia in the adolescent population has not been systematically evaluated. However, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients.
Or, as prescribed by a physician.	

Prudent long-term treatment options in adult patients with schizophrenia with remitted first episodes or multiple episodes include either indefinite maintenance therapy or gradual discontinuation of the antipsychotic agent with close follow-up and a plan to reinstitute treatment upon symptom recurrence.

Discontinuance of antipsychotic therapy should be considered only after a period of at least 1 year of symptom remission or optimal response while receiving the antipsychotic agent. In patients who have had multiple previous psychotic episodes or 2 psychotic episodes within 5 years, indefinite maintenance antipsychotic treatment is recommended.

Bipolar I Disorder (Manic or Mixed Episodes)

Usual Recommended Olanzapine Oral Dose	
INITIAL TREATMENT	
Adults (≥ 18 years old)	**Adolescents (13 to 17 years old)**
Recommended starting dose as monotherapy: 10 or 15 mg/day Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours. When dosage adjustments are necessary, dose increments/decrements of 5 mg/day are recommended **Recommended starting dose as adjunctive treatment to lithium or valproate:** 10 mg/day Antimanic efficacy was shown in a dose range of 5 to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials ***Preventing recurrence in Bipolar I Disorder*** **Recommended starting dose: 10 mg/day** If a new manic, mixed, or depressive episode occurs, olanzapine should be continued (with dose optimization as needed), with supplementary therapy to treat mood symptoms, as clinically indicated For patients already in remission, the recommended starting olanzapine dose is 10 mg once a day Subsequent adjustment of daily dosage should be based on clinical status within a range of 5 to 20 mg/day An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours	**Recommended starting dose:** 2.5 or 5 mg/day, with a target dose of 10 mg/day. When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended. The safety and efficacy of doses above 20 mg/day have not been evaluated in clinical trials.
MAINTENANCE TREATMENT It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.	
The benefit of maintaining Bipolar I patients on monotherapy with oral olanzapine at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of two weeks, was shown in a controlled trial.	The efficacy of olanzapine for the maintenance treatment of Bipolar I Disorder in the adolescent population has not been evaluated. However, maintenance efficacy can be extrapolated from adult data along with comparison of olanzapine pharmacokinetic parameters in adult and adolescent patients.
Or, as prescribed by a physician.	

Olanzapine in Combination with Fluoxetine

DEPRESSIVE EPISODES ASSOCIATED WITH BIPOLAR I DISORDER	
INITIAL TREATMENT	
Adults(≥ 18 years old)	**Children and Adolescents (10 to 17 years old)**
Initial dose: Olanzapine 5 mg and fluoxetine 20 mg once a day in the evening, with or without food Dosage adjustments, if indicated, can be made based on efficacy and tolerability within the dose ranges of olanzapine 5 to 12.5 mg and fluoxetine 20 to 50 mg Antidepressant efficacy was shown with olanzapine and fluoxetine in combination with a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg Safety of co-administration of doses above olanzapine 18 mg with fluoxetine 75 mg has not been evaluated in clinical studies	**Initial dose:** Olanzapine 2.5 mg and fluoxetine 20 mg once a day in the evening, with or without food Dosage adjustments, if indicated, can be made based on efficacy and tolerability Safety of co-administration of doses above olanzapine 12 mg with fluoxetine 50 mg has not been evaluated in pediatric clinical studies
MAINTENANCE/ CONTINUATION/ EXTENDED TREATMENT While there is no body of evidence to answer the question of how long a patient treated with olanzapine and fluoxetine in combination should remain on it, it is generally accepted that Bipolar I Disorder, including depressive episodes associated with Bipolar I Disorder, is a chronic illness requiring chronic treatment. The physician should periodically re-examine the need for continued pharmacotherapy.	
Or, as prescribed by a physician.	

TREATMENT RESISTANT DEPRESSION
INITIAL TREATMENT
Adults (≥ 18 years old)
Initial dose: Olanzapine 5 mg and fluoxetine 20 mg once a day in the evening, with or without food Dosage adjustments, if indicated, can be made based on efficacy and tolerability within the dose ranges of olanzapine 5 to 20 mg and fluoxetine 20 to 50 mg Antidepressant efficacy was shown with fluoxetine and olanzapine in combination with a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies
MAINTENANCE/ CONTINUATION/ EXTENDED TREATMENT While there is no body of evidence to answer the question of how long a patient treated with fluoxetine and olanzapine in combination should remain on it, it is generally accepted that treatment resistant depression is a chronic illness requiring chronic treatment. The physician should periodically re-examine the need for continued pharmacotherapy.
Or, as prescribed by a physician.

Special Populations:
Elderly (≥ 65 years old):
Recommended Olanzapine Starting Dose: 5 mg/day
When necessary, increase in dose should be done with caution in these patients.

Patients with Hepatic and/or Renal Impairment:
Recommended Olanzapine Starting Dose: 5 mg/day
Further dose adjustments, when indicated, should be conservative in these patients.

Smokers:
The starting dose and dose range of olanzapine need not be routinely altered for non-smokers relative to smokers.
Consideration should be given to decreasing the starting dose, when more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status). Dose escalation, when indicated, should be conservative in these patients.

Debilitated patients, patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or olanzapine and fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine:

Recommended Olanzapine Starting Dose for Schizophrenia:
5 mg; when indicated, dose escalation should be performed with caution in these patients.

Recommended Olanzapine in Combination with Fluoxetine Starting Dose:
Olanzapine 2.5 to 5 mg with fluoxetine 20 mg

Dose modification may be necessary in patients who exhibit a combination of factors that may slow metabolism.

When indicated, dose escalation should be done with caution in these patients.
Olanzapine and fluoxetine in combination have not been systematically studied in patients over 65 years old or in patients below 10 years old.

Or, as prescribed by a physician.

CONTRAINDICATION
- Hypersensitivity to olanzapine or any ingredient of the product

WARNINGS AND PRECAUTIONS

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

General
During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period. When using olanzapine in combination with fluoxetine, lithium or valproate, also refer to their individual product literature for additional information.

Neuroleptic Malignant Syndrome (NMS): There have been reports of NMS, a potentially fatal symptom complex, in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine kinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. Careful monitoring of patients is necessary since recurrences of NMS have been reported.

Weight Gain: Potential consequences of weight gain should be considered before starting olanzapine. As with all antipsychotics, patients receiving olanzapine should receive regular monitoring of weight.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been associated with the use of antipsychotic agents. Exercise caution when giving olanzapine to patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

Potential for Cognitive and Motor Impairment: Since olanzapine has the potential to cause somnolence and impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Cardiovascular Effects
Orthostatic Hypotension: Patients receiving oral olanzapine therapy are reported to develop orthostatic hypotension associated with dizziness, tachycardia, and/or syncope, particularly at the initiation of treatment. The risk of orthostatic hypotension and syncope may be minimized by initiating therapy with a dose of 5 mg orally once a day. If hypotension occurs, a more gradual titration to the target dose should be considered.

Olanzapine should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Sudden Cardiac Death: Retrospective observational study showed patients treated with atypical antipsychotics, including olanzapine, or typical antipsychotics had a similar dose-related increase of presumed sudden cardiac death compared to non-users of antipsychotics, with almost twice the risk than that for non-users. In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported very rarely.

Cerebrovascular Effects: Cerebrovascular adverse events such as stroke and transient ischemic attack, including fatalities, were reported in elderly patients with dementia-related psychosis taking olanzapine.

QT Interval: As with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines known to increase QT_c interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia or hypomagnesemia. Clinically meaningful QT_c prolongations were uncommon in patients treated with olanzapine.

Endocrine and Metabolic Effects
Hyperglycemia and Diabetes Mellitus: Physicians 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 to 126 mg/dL, nonfasting 140 to 200 mg/dL). Patients should have baseline and periodic monitoring of blood glucose and body weight.

There have been reports of severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, in patients receiving certain atypical antipsychotic agents 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.

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 was resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels and a modest elevation persists during chronic administration. Elevations associated with olanzapine treatment are generally mild, and may decline during continued administration.

Hyperprolactinemia may suppress hypothalamic gonadotropin-releasing hormone (GnRH), resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. Premenopausal women should be questioned on menstrual irregularities and those who experience secondary amenorrhea for longer than six months duration while taking olanzapine, should be appropriately investigated and offered appropriate therapy.

Hyperlipidemia: Undesirable alterations in lipids have been observed with olanzapine use. Treatment-emergent clinically significant changes in fasting lipids were observed in patients with or without evidence of dyslipidemia at baseline. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using olanzapine, is recommended.
Clinically significant and sometimes very high (> 500 mg/dL) elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Hematologic Effects
Leukopenia, Neutropenia, and Agranulocytosis: Events of leukopenia/neutropenia temporally related to antipsychotic agents, including olanzapine have been reported. Agranulocytosis has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of olanzapine should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1,000/mm3) should discontinue olanzapine and have their WBC followed until recovery.

Hepatic Effects
Transient, asymptomatic elevations of hepatic aminotransferases, alanine transaminase (ALT), aspartate aminotransferase (AST) have been reported commonly, particularly in early treatment. Caution should be exercised and follow-up organized in patients with: elevated ALT and/or AST, signs and symptoms of hepatic impairment, pre-existing conditions associated with limited hepatic functional reserve, and who are being treated with potentially hepatotoxic medicines. Olanzapine treatment should be discontinued in cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed.

Nervous System Effects
Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, patients are likely to develop the syndrome at the inception of antipsychotic treatment. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drug products administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief periods at low doses or may even arise after discontinuation of treatment.

Comparator studies of one year or less duration showed that olanzapine was associated with a statistically lower incidence of treatment emergent dyskinesia. However, the risk of tardive dyskinesia increases with long-term exposure and thus, if signs or symptoms of tardive dyskinesia appear in a patient on olanzapine, a dose reduction or drug discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment. Some patients may require treatment with olanzapine despite the presence of the syndrome.

Seizures: Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold (e.g., Alzheimer's dementia). Conditions that lower the seizure threshold may be more prevalent in a population of ≥ 65 years old. Seizures have been reported to occur rarely in such patients when treated with olanzapine.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder. Close supervision of high-risk patients should accompany drug therapy.
Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Respiratory Effects
Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic use. Olanzapine and other antipsychotic agents should be used cautiously in patients at risk for aspiration pneumonia. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine is not approved for the treatment of patients with Alzheimer's disease.

Use in Patients with Concomitant Illness
Since clinical experience with olanzapine in patients with concomitant illness is limited, caution is advised when prescribing in patients with prostatic hypertrophy, narrow-angle glaucoma, or a history of paralytic ileus or related conditions because of the anticholinergic effects of olanzapine. It should also be used with caution in patients with hepatic impairment, or a history of blood dyscrasias, bone marrow depression, or myeloproliferative disease.

INTERACTION WITH OTHER MEDICAMENTS
Alcohol: Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The coadministration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine.
Antihypertensive agents: Olanzapine, because of its potential for inducing hypotension, may enhance the effects of certain antihypertensive agents.
Carbamazepine: Causes an approximately 50% increase in olanzapine clearance; this increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity.
Activated charcoal: The use of activated charcoal (1 g) reduced the C_{max} and area under the plasma concentration time curve (AUC) of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about six hours after dosing, charcoal may be a useful treatment for olanzapine overdose.
Central nervous system (CNS) acting drugs: Caution should be used when olanzapine is taken in combination with other CNS acting drugs and alcohol.
Diazepam: The coadministration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine.
Fluoxetine: Causes a small increase in the maximum concentration of olanzapine and a small decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and thus dose modification is not routinely recommended.
Fluvoxamine: Decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} after fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.
Levodopa and dopamine agonists: Olanzapine may antagonize the effects of levodopa and dopamine agonists.
Omeprazole and rifampicin: May cause an increase in olanzapine clearance.
Biperiden and theophylline: Did not influence the kinetics of biperiden and theophylline.
Cimetidine and antacids: Single doses of cimetidine or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.
Drug metabolizing enzymes: *In vitro* studies utilizing human liver microsomes showed that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.
Imipramine/desipramine: Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.
Lithium: Multiple doses of olanzapine did not influence the kinetics of lithium. Concomitant olanzapine use does not require dosage adjustment of lithium.
Valproate: Olanzapine did not affect the steady state plasma concentrations of valproate. Concomitant olanzapine use does not require dosage adjustment of valproate.
Warfarin: Did not affect olanzapine pharmacokinetics.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy and Lactation
Pregnancy Category C. There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including two resulting in normal births, one resulting in neonatal death due to a cardiovascular defect, three therapeutic abortions, and one spontaneous abortion.

Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms after delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Patients should notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. Olanzapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery. The effect of olanzapine on labor and delivery in humans is unknown.

Breastfeeding. In a study of breastfeeding, healthy women, olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady-state was estimated to be 1.8% of the maternal olanzapine dose (mg/kg). Patients should be advised not to breastfeed an infant if they are taking olanzapine.

Pediatric (< 18 years old)
When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents.

The safety and efficacy of olanzapine in children <13 years old have not been established.

The safety and efficacy of olanzapine and fluoxetine in combination in children >10 years old have not been established.

Geriatric (≥ 65 years old)
Exercise caution with the use of olanzapine in the elderly patient, recognizing the more frequent hepatic, renal, central nervous system, and cardiovascular dysfunctions, and more frequent use of concomitant medication in this population (see Pharmacokinetics and Dosage and Administration for Special Populations and Warnings and Precautions).

UNDESIRABLE EFFECTS
Body as a whole: *Very common* - Falls in the elderly. *Common* - Accidental injury, fever, back pain, pain in extremity, asthenia, fatigue. *Uncommon* - Chills, face edema. *Rare* - Chills and fever, neck pain, neck rigidity. *Unknown* - Hypothermia, neonatal drug withdrawal syndrome
Cardiovascular: *Common* - Postural hypotension, chest pain, tachycardia, hypertension. *Uncommon* - Bradycardia, cerebrovascular accident, vasodilation, QT_c prolongation, venous thromboembolism (including pulmonary embolism and deep vein thrombosis), syncope. *Unknown* - Ventricular tachycardia/fibrillation
Endocrine and Metabolic: *Very Common* - Weight gain, elevated prolactin. *Common* - Increased appetite, peripheral edema, edema, glycosuria, elevated cholesterol levels, hyperglycemia, elevated triglyceride levels, elevated creatine kinase levels, increased uric acid levels. *Uncommon* - Bilirubinemia, hypoproteinemia, decreased libido, impotence, increased alkaline phosphatase acidosis, hypoglycemia, hypokalemia, hyponatremia, lower or upper extremity edema. *Rare* - Exacerbation of pre-existing diabetes, goiter, gout, hypernatremia, ketosis, water intoxication. *Unknown* - Diabetic coma, diabetic ketoacidosis
Gastrointestinal: *Common* - Mild transient anticholinergic effects (e.g.,constipation, dry mouth), dyspepsia, vomiting, increased salivation, thirst, nausea, abdominal pain, diarrhea, flatulence. *Uncommon* - Nausea and vomiting, tongue edema, abdominal distension, dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, melena, mouth ulceration, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tooth caries. *Rare* - Ileus, intestinal obstruction, aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, tongue discoloration. *Unknown* - Pancreatitis
Hematologic: *Common* - Ecchymosis, eosinophilia. *Uncommon* - Leukopenia, neutropenia. *Unknown* - Thrombocytopenia
Hepatic: *Common* - Increased liver enzymes (ALT, AST). *Rare* - Fatty deposit in the liver. *Very Rare* - Cholestatic or mixed liver injury, *Unknown* - Jaundice, hepatic failure, hepatitis (including hepatocellular)
Musculoskeletal: *Common* - Extremity pain (other than joint), joint pain, arthralgia, musculoskeletal stiffness, twitching. *Uncommon* - Arthritis, arthrosis, leg cramps, myasthenia. *Rare* - Osteoporosis, bone pain, bursitis, myopathy, rheumatoid arthritis, rhabdomyolysis
Nervous system: *Common* - Dizziness, personality disorder, akathisia, somnolence, tremor, insomnia, abnormal gait, hypertonia, articulation impairment, speech disorder, amnesia, paresthesia, depression, apathy, confusion, euphoria, incoordination, extrapyramidal symptoms (dystonic, parkinsonism, dyskinetic, and residual events), sedation, headache, restlessness, agitation, hostility, anxiety, neurosis, hallucinations, abnormal dreams, delusions, emotional lability, manic reaction, schizophrenic reaction. *Uncommon* - Suicide attempt, ataxia, dysarthria, stupor, seizures, alcohol misuse, antisocial reaction, CNS stimulation, delirium, dementia, depersonalization, facial paralysis, hypesthesia, hypokinesia, obsessive-compulsive symptoms, phobias, somatization, stimulant misuse, stuttering, vertigo, withdrawal syndrome (diaphoresis, nausea or vomiting). *Rare* - Hangover effect, sudden death, coma, circumoralparesthesia, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. *Unknown* - NMS, tardive dyskinesia
Respiratory: *Common* - Rhinitis, increased cough, pharyngitis, dyspnea, nasopharyngitis, respiratory tract infection, sinusitis. *Uncommon* - Epistaxis, apnea, asthma, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration. *Rare* - Lung edema, atelectasis, hiccup, hypoventilation, stridor
Skin and appendages: *Common* - Sweating, acne, dry skin, fungal dermatitis, rash. *Uncommon* - Photosensitivity reaction, alopecia, contact dermatitis, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration (e.g., hyperpigmentation), skin ulcer, urticarial, vesiculobullous rash. *Rare* - Hirsutism, pustular rash. *Unknown* - Allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus, or urticaria), eruptive xanthomas, leukocytoclasticvasculitis
Special Senses: *Common* - Amblyopia, abnormal vision, blepharitis, conjunctivitis, corneal lesion. *Uncommon* - Abnormality of accommodation, dry eyes, cataract, deafness, diplopia, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, tinnitus, taste perversion. *Rare* - Mydriasis, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, pigment deposits in the eye lens
Urogenital: *Common* - Urinary incontinence, urinary tract infection, dysmenorrhea, vaginitis, erectile dysfunction in males. *Uncommon* - Amenorrhea, breast pain, breast enlargement, galactorrhea in females, decreased or increased menstruation, menorrhagia, metrorrhagia, polyuria, urinary frequency, urinary retention, urinary urgency, impaired urination, abnormal ejaculation, cystitis, dysuria, hematuria, premenstrual syndrome, pyuria, enlarged uterine fibroids, vaginal hemorrhage, pelvic pain. *Rare* - Albuminuria, mastitis, oliguria. *Unknown* - Urinary hesitation, priapism

OVERDOSE AND TREATMENT
Very common symptoms reported for olanzapine overdose include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms and reduced level of consciousness ranging from sedation to coma. Other significant symptoms of overdose include delirium, convulsion, possible NMS, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias, and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg, however, survival has also been reported following acute oral overdose of approximately 2 g.

There is no specific antidote to olanzapine. Induction of emesis is not recommended. Standard procedures for the management of overdose may be given. The possibility of multiple drug involvement should also be considered.

During acute overdose, airway should be established and maintained. Ensure also that there is adequate oxygenation and ventilation. The use of activated charcoal for overdose should be considered because the concomitant use of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50% to 60%. In patients who are not fully conscious or who have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Olanzapine is not substantially removed by hemodialysis.

Symptomatic treatment and monitoring of vital organ function should be done according to clinical presentation, such as treatment of hypotension and circulatory collapse and support of respiratory function. Appropriate measures such as intravenous fluids and/or sympathomimetic agents (e.g., noradrenaline) should be given to treat hypotension and circulatory collapse. Adrenaline, dopamine or other sympathomimetic agents should not be used since beta stimulation may worsen hypotension in the setting of α-blockade induced by olanzapine. Cardiovascular monitoring should be considered to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

ADR Reporting Statement
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C. Keep the product out of sight and reach of children.

AVAILABILITY
Olanzapine (Salveo) 10 mg film-coated tablet – Alu-Alu Blister Foil x 4's (Box of 28's) - DR-XY39353

CAUTION
Foods, Drugs, Devices, and Cosmetics Act Prohibits dispensing without prescription.

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