Front

ZAP
(Olanzapine)

TABLET

زیپ

COMPOSITION:
ZAP Tablet 5 mg:
Each film coated tablet contains:
Olanzapine ..... 5 mg.

Product Specs.: USP

ZAP Tablet 10 mg:
Each film coated tablet contains:
Olanzapine ..... 10 mg.

Product Specs.: USP

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.
- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZAP is not approved for the treatment of patients with dementia-related psychosis.

When using ZAP and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.

DESCRIPTION:
ZAP (olanzapine) is an atypical antipsychotic that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b] [1,5] benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:

CLINICAL PHARMACOLOGY:
Mechanism of Action:
The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism. The mechanism of action of olanzapine in the treatment of acute manic or mixed episodes associated with bipolar I disorder is unknown.

Pharmacokinetics:
Oral Administration, Monotherapy — Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZAP tablets and dosage forms of olanzapine are bioequivalent. Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr). Administration of olanzapine once daily leads to steady-state concentrations in about 1 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, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and α1-acid glycoprotein.
Metabolism and excretion:
Following a single oral dose of 14C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4′-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed. Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Special Populations:
Pregnancy:
Teratogenic Effects, Pregnancy Category C — In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily oral dose on a mg/m2 basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a mg/m2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m2 basis). In an oral rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the maximum recommended human daily oral dose on a mg/m2 basis). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Placental transfer of olanzapine occurs in rat pups. There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion
Nonteratogenic Effects — Neonates exposed to antipsychotic drugs (including ZAP), during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following 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. ZAP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
Nursing mothers:
In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.
Renal impairment:
Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied
Hepatic impairment:
Although 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 (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.
Pediatric use:
The safety and effectiveness of oral ZAP in the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder were established in short-term studies in adolescents (ages 13 to 17 years). Use of ZAP in adolescents is supported by evidence from adequate and well-controlled studies of ZAP in which 268 adolescents received ZAP in a range of 2.5 to 20 mg/day. Recommended starting dose for adolescents is lower than that for adults. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic aminotransferase levels. 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 dyslipidemia. 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.
Geriatric use:
Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia related psychosis treated with olanzapine are at an increased risk of death compared to placebo. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric Clinical studies of ZAP and fluoxetine in combination did not include sufficient numbers of patients ⩾65 years of age to determine whether they respond differently from younger patients.

INDICATIONS AND USAGE:
Schizophrenia:
Oral ZAP is indicated for the treatment of schizophrenia. Efficacy was established in three clinical trials in adult patients with schizophrenia: two 6-week trials and one maintenance trial. In adolescent patients with schizophrenia (ages 13-17), efficacy was established in one 6-week trial. 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 dyslipidemia. 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.
Bipolar I Disorder (Manic or Mixed Episodes) Monotherapy: Oral ZAP is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. Efficacy was established in three clinical trials in adult patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one monotherapy maintenance trial. In adolescent patients with manic or mixed episodes associated with bipolar I disorder (ages 13-17), efficacy was established in one 3-week trial. 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 dyslipidemia. 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. Adjunctive Therapy to Lithium or Valproate — Oral ZAP is indicated for the treatment of manic or mixed episodes associated with bipolar I disorder as an adjunct to lithium or valproate. Efficacy was established in two 6-week clinical trials in adults. The effectiveness of adjunctive therapy for longer-term use has not been systematically evaluated in controlled trials.
Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder Pediatric: Schizophrenia and bipolar I disorder are serious mental disorders; however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, pediatric patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder should be part of a total treatment program that often includes psychological, educational and social interventions.

DOSAGE AND ADMINISTRATION:
Schizophrenia
Adults:
Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended. Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. Olanzapine is not indicated for use in doses above 20 mg/day.
Dosing in Special Populations:
The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ⩾65 years of age), or who may be more pharmacodynamically sensitive to. When indicated, dose escalation should be performed with caution in these patients.
Maintenance Treatment — The effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZAP for approximately 8 weeks and were then followed for relapse has been demonstrated in a placebo-controlled trial. The physician who elects to use ZAP for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.
Adolescents:
Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents

with schizophrenia was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 12.5 mg/day (mean dose of 11.1 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended. The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials.
Maintenance Treatment — The efficacy of ZAP 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. Thus, 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.

Bipolar I Disorder (Manic or Mixed Episodes):
Adults:
Dose Selection for Monotherapy — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended. Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.
Maintenance Monotherapy — The benefit of maintaining bipolar I patients on monotherapy with oral ZAP at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of 2 weeks, was demonstrated in a controlled trial. The physician who elects to use ZAP for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.
Dose Selection for Adjunctive Treatment — When administered as adjunctive treatment to lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals. Antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.
Adolescents:
Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with bipolar I disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended. The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials.
Maintenance Treatment — The efficacy of ZAP 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 comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, 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.

----------DOSAGE AND ADMINISTRATION----------

Schizophrenia in adults	Oral: Start at 5-10 mg once daily; Target: 10 mg/day within several days
Schizophrenia in adolescents	Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day
Bipolar I Disorder (manic or mixed episodes) in adults	Oral: Start at 10 or 15 mg once daily
Bipolar I Disorder (manic or mixed episodes) in adolescents	Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day
Bipolar I Disorder (manic or mixed episodes) with lithium or valporate in adults	Oral: Start at 10 mg once daily
Agitation associated with Schizophrenia and Bipolar I Mania in adults	IM: 10 mg (5 mg or 7.5 mg when clinically warranted Assess for orthostatic hypotension prior to subsequent dosing (max. 3 doses 2-4 hrs apart)
Depressive Episodes associated with Bipolar I Disorder in adults	Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluuoxetine once daily
Depressive Episodes associated with Bipolar I Disorder in children and adolescents	Oral in combination with fluoxetine: Start at 2.5 mg of oral olanzapine and 20 mg of fluuoxetine once daily
Treatment Resistant Depression in adults	Oral in combination with fluoxetine: Start at5 mg of oral olanzapine and 20 mg of fluuoxetine once daily

CONTRAINDICATIONS:
None with ZAP monotherapy.
- When using ZAP and fluoxetine in combination, also refer to the Contraindications section of the package insert for Olanzapine/fluoxetine.
- For specific information about the contraindications of lithium or valproate, refer to the Contraindications section of the package inserts for these other products.

WARNINGS AND PRECAUTIONS:
Elderly Patients with Dementia-Related Psychosis:
Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) Cerebrovascular Adverse Events (CVAE), Including Stroke Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Patient Counseling Information (17.2)].
Suicide:
The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy; when using in combination with fluoxetine
Neuroleptic Malignant Syndrome (NMS):
Manage with immediate discontinuation and close monitoring
Metabolic Changes:
Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia, and weight gain.
Hyperglycemia and Diabetes Mellitus: In some cases, extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking olanzapine. Patients taking olanzapine should be monitored for symptoms of hyperglycemia and undergo fasting blood glucose testing at the beginning of, and periodically during, treatment.
Dyslipidemia: Undesirable alterations in lipids have been observed. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically during, treatment.
Weight Gain: Potential consequences of weight gain should be considered. Patients should receive regular monitoring of weight.
Tardive Dyskinesia: Discontinue if clinically appropriate
Orthostatic Hypotension: Orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, may occur especially during initial dose titration. Use caution in patients with cardiovascular disease, cerebrovascular disease, and those conditions that could affect hemodynamic responses
Leukopenia, Neutropenia, and Agranulocytosis: Has been reported with antipsychotics, including ZAP. Patients with a history of a clinically significant low white blood cell count (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 ZAP should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors
Seizures: Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.9) • Potential for Cognitive and Motor Impairment: Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery
Hyperprolactinemia: May elevate prolactin levels. (5.13) • Use in Combination with Fluoxetine, Lithium or Valproate: Also refer to the package inserts for Olanzapine/fluoxetine, lithium, or valproate
Laboratory Tests: Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment

ADVERSE REACTIONS:
Most common adverse reactions (⩾5% and at least twice that for placebo) associated with:
Oral Olanzapine Monotherapy:
Schizophrenia (Adults) – postural hypotension, constipation, weight gain, dizziness, personality disorder, akathisia (6.1)
Schizophrenia (Adolescents) – sedation, weight increased, headache, increased appetite, dizziness, abdominal pain, pain in extremity, fatigue, dry mouth
Manic or Mixed Episodes, Bipolar I Disorder:
(Adults) – asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor
Manic or Mixed Episodes, Bipolar I Disorder:
(Adolescents) – sedation, weight increased, increased appetite, headache, fatigue, dizziness, dry mouth, abdominal pain, pain in extremity
Combination of ZAP and Lithium or Valproate:
Manic or Mixed Episodes, Bipolar I Disorder (Adults) – dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia

DRUG INTERACTIONS:
- ***Diazepam:*** May potentiate orthostatic hypotension
- ***Alcohol:*** May potentiate orthostatic hypotension
- ***Carbamazepine:*** Increased clearance of olanzapine
- ***Fluvoxamine:*** May increase olanzapine levels
- ***ZAP and Fluoxetine in Combination:*** Also refer to the Drug Interactions section of the package insert for Olanzapine/fluoxetine
- ***CNS Acting Drugs:*** Caution should be used when taken in combination with other centrally acting drugs and alcohol.
- ***Antihypertensive Agents:*** Enhanced antihypertensive effect.
- ***Levodopa and Dopamine Agonists:*** May antagonize levodopa/dopamine agonists.
- ***Lorazepam (IM):*** Increased somnolence with IM olanzapine.
- ***Other Concomitant Drug Therapy:*** When using olanzapine in combination with lithium or valproate, refer to the Drug Interactions sections of the package insert for those products.

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight and moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

PRESENTATION:
ZAP Tablet 5 mg : Pack of 1 x 10 tablets.
ZAP Tablet 10 mg : Pack of 1 x 10 tablets.

FOR FURTHER INFORMATIONS PLEASE CONTACT:

CCL
Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.

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