PRANZA®

Olanzapine

ACTION

Olanzapine is antipsychotic, antimanic and mood stabilizing agent that demonstrates a broad pharmacologic profile across a number of receptor systems exhibiting a range of receptor affinities for serotonin 5HT2A/2C, 5HT3, 5HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors M1-M5; α1 adrenergic; and histamine H1 receptors.

INDICATIONS

- Pranza is indicated for acute and maintenance treatment of schizophrenia and other psychosis where positive symptoms (e.g. delusions, hallucinations, disordered thinking, hostility, and suspiciousness) and/or negative symptoms (e.g. flattened affect, emotional and social withdrawal, poverty of speech) are prominent. Pranza also alleviates secondary affective symptoms commonly associated with schizophrenia and related disorders. Pranza is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
- Pranza is indicated for the treatment of moderate to severe manic episodes.
- In patients whose manic episode has responded to Pranza treatment, Pranza is indicated for prevention of recurrence in patients with bipolar disorder.

DOSAGE AND ADMINISTRATION

Schizophrenia: the recommended starting dose for Pranza is 10 mg/day.

Manic episode: the starting dose for Pranza is 15 mg as a single daily dose in monotherapy or 10 mg daily in combination therapy.

Preventing recurrence in bipolar disorder: the recommended starting dose for Pranza is 10 mg/day. For patients who have been receiving Pranza for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, Pranza therapy should be continued (with dose optimization as needed), with supplementary therapy to treat mood symptoms, as clinically indicated. During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20 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 interval of not less than 24 hours. Pranza can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing Pranza.

Adolescence and Pediatric Use:

When deciding among the prescribing information 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.

Need for comprehensive treatment program in pediatric patients: Olanzapine is indicated as an integral part of a total treatment program for pediatric patients with schizophrenia and bipolar disorder that may include other measures (psychological, educational, and social) for patients with the disorder. Effectiveness and safety of olanzapine have not been established in pediatric patients less than 13 years of age.

Elderly patients: A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factor warrant.

Patients with renal and/or hepatic impairment: A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.

Gender: The starting dose and dose range need not to be routinely altered for female patients relative to male patients.

Smokers: The starting dose range need not to be routinely altered for non-smokers relative to smokers.

Note: When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be giving to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. Patients with known risk for narrow-angle glaucoma.

WARNINGS AND PRECAUTIONS

Hyperglycemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable particularly in diabetic patients and in patients with risk factors for development of diabetes mellitus for which regular glucose control is recommended.

Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo controlled clinical trials. Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipid disorders.

Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea or vomiting have been reported very rarely (<0.01%) when olanzapine is stopped abruptly. Gradual dose reduction should be considered when discontinuing olanzapine. As clinical experience with olanzapine in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy or paralytic ileus and related conditions.

The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. Olanzapine is not approved for dementia-related psychosis and/or behavioral disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. Risk factors that may predispose this patient population to increase mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g. pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated patients than in placebo-treated patients independent of these risk factors.

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.

Transient asymptomatic elevation of hepatic transaminases, ALT, AST has been seen commonly, especially in early treatment. Caution should be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with preexisting conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicines treatment. In the event of elevated ALT and/or AST during treatment, follow up should be organized and dose reduction should be considered. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

As with other neuroleptic medicines, caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly.

There are limited data on co-medication with lithium and valproate. There are no clinical data available on olanzapine and carbamazepine co-therapy; however a pharmacokinetic has been conducted).

Neuroleptic malignant syndrome (NMS): NMS is a potentially life-threatening condition associated with antipsychotic medication. Rare cases reported as NMS has also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and the evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (Rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or present with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.

Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures was reported.

Tardive Dyskinesia: In comparator studies in one year or less duration, olanzapine was associated with statistically significant lower incidence of treatment emergent dyskinesia. However the risk of tardive dyskinesia increases with long term exposure, and therefore if signs or symptoms of tardive dyskinesia appear in a patient on olanzapine, a dose reduction or discontinuation should be considered. These symptoms can temporary deteriorate or even arise after discontinuation of treatment.

Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting medicines and alcohol. As it exhibits in vitro dopamine antagonism, olanzapine may antagonize the effects of direct and indirect dopamine agonists.

Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. As with other antipsychotics, it is recommended that blood pressure is measured periodically in patients over 65 years.

As with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines know to increase QTc interval, especially in elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia or hypomagnesaemia.

Since patients with schizophrenia often present with acquired risk factors for venous thromboembolism, all possible risk factors of VTE (e.g., immobilization of patients) should be identified and preventive measures undertaken.

Phenylalanine: Olanzapine ODT tablet contains aspartame, which is a source of phenylalanine. May be harmful for people with phenylketonuria.

Mannitol: Olanzapine ODT tablet contains mannitol.

Pregnancy and Lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. Nevertheless, because human experience is limited, olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

There is potential risk for abnormal muscle movements (extrapyramidal signs or EPS) and withdrawal symptoms in newborns whose mothers were treated with these drugs during the third trimester of pregnancy. The symptoms of EPS and withdrawal in newborns may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty in feeding. In some newborns, the symptoms subside within hours or days and do not require specific treatment; other newborns may require longer hospital days.

Recommendation: Healthcare professionals should be aware of the effects of antipsychotic medications on newborns when the medications are used during pregnancy. Patients should not stop taking these medications if they become pregnant without talking to their healthcare professional, as abruptly stopping antipsychotic medications can cause significant complications for treatment.

Lactation

Patients should be advised not to breast feed an infant if they are taking olanzapine.

Effects on ability to Drive and use machines

No studies of the effects of the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

Alcohol

Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with alcohol.

Drug Interactions

Caution should be exercised in patients who receive medicinal products that can cause central nervous system depression.

Potential interactions affecting olanzapine: Since olanzapine is metabolized by CYP1A2, substances that can specifically induce or inhibit this isoenzyme may affect the pharmacokinetics of olanzapine.

Induction of CYP1A2: The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary.

Inhibition of CYP1A2: Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

Decrease bioavailability: activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60% and should be taken at least 2 hours before or after olanzapine.

Fluoxetine (a CYP2D6 inhibitor), single doses of antacids (aluminum, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.

Potential for olanzapine to affect other medicinal products: Olanzapine may antagonize the effects of direct and indirect dopamine antagonists.

Olanzapine does not inhibit the main CYP450 isoenzymes in vitro (e.g., 1A2, 2D6, 2C9, 2C19, 3A4). Thus no particular interaction is expected as verified through in vivo studies where no inhibition of metabolism of the following active substances was found: tricyclic antidepressants (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19).

Olanzapine showed no interaction when co-administered with lithium or biperiden.

Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant of olanzapine.

SIDE EFFECTS

Very common (> 10%) undesirable effects associated with the use of olanzapine in clinical trials were somnolence and weight gain.

In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse events compared to placebo. Very common (> 10%) undesirable effects associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increase body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly (1-10%).

In clinical trials in patients with drug induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening in Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%, a potential contribution factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥ 10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly (1%-10%).

The following are adverse effects based on adverse event reporting and laboratory investigations from clinical trials:

Blood and lymphatic system disorders

Common (1-10%): Eosinophilia.

Metabolism and nutrition disorders

Very common (> 10%): Weight gain.

Common (1-10%): Increased appetite. Elevated glucose levels. Elevated triglyceride levels. Elevated cholesterol levels. Glycosuria.

Nervous system disorders

Very common (> 10%): Somnolence.

Common (1-10%): Dizziness. Akathisia. Parkinsonism. Dyskinesia.

Cardiac disorders

Uncommon (0.1-1%): Bradycardia with or without hypotension or syncope. QT prolongation.

Vascular disorders

Common (1-10%): Orthostatic hypotension.

Gastrointestinal disorders

Common (1-10%): Mild transient anticholinergic effects including constipation and dry mouth.

Hepato-biliary disorders

Common (1-10%): Transient asymptomatic elevations of hepatic transaminases (ALT,AST) especially in early treatment.

Skin and subcutaneous tissue disorders

Uncommon (0.1-1%): Photosensitivity reactions.

General disorders and administration site reactions

Common (1-10%): Asthenia. Fatigue. Oedema.

Investigations

Very common (> 10%): Elevated plasma prolactin levels, but associated clinical manifestations (e.g., gynaecomastia, galactorrhoea, and breast enlargement) were rare. In most patients levels returned to normal ranges without cessation of treatment.

Uncommon (0.1-1%): High creatine phosphokinase.

OVERDOSAGE

Signs and symptoms

Very common symptoms in overdose (> 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms and reduced level of consciousness ranging from sedation to coma. Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of 1500 mg.

Management of overdose

There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50-60%. Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypertension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

STORAGE

Store below 30°C, away from light and moisture.

PRESENTATIONS

Orodispersible tablets

PRANZA 5: Olanzapine 5 mg/tablet

PRANZA 10: Olanzapine 10 mg/tablet

Excipients: Microcrystalline cellulose, mannitol, pregelatinized starch, aspartame, crospovidone, sodium lauryl sulphate, colloidal silicon dioxide, magnesium stearate, lemon flavor.

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

HIKMA

Manufactured by:
HIKMA Pharmaceuticals, Amman-Jordan

Keep medicament out of the reach of children

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