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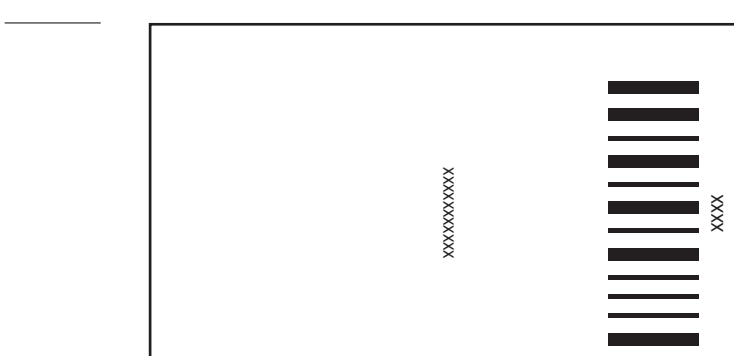


hovid

Hovid Olanzapine Orodispersible Tablets

VIOLA01-var2 (MY)

DESCRIPTION

Hovid Olanzapine Orodispersible Tablets 5mg: Yellow coloured, round, flat face bevelled edge tablets with characteristic flavour, debossed with “D5” on one side and “CO” on other side.

Hovid Olanzapine Orodispersible Tablets 10mg: Yellow coloured, round, flat face bevelled edge tablets with characteristic flavour, debossed with “D10” on one side and “CO” on other side.

COMPOSITION

Hovid Olanzapine Orodispersible Tablets 5mg: Each orodispersible tablet contains Olanzapine Ph. Eur. 5mg.

Hovid Olanzapine Orodispersible Tablets 10mg: Each orodispersible tablet contains Olanzapine Ph. Eur. 10mg.

ACTIONS AND PHARMACOLOGY

The exact mechanism by which olanzapine exerts its antipsychotic effect is unknown. Olanzapine is a selective monoaminergic antagonist with a strong affinity for serotonin 5-HT_{2A} and 5-HT_{2C} receptors, and dopamine D_1, D_2, D_3, and D_4 receptors. It weakly binds to gammaaminobutyric acid type A ($GABA_A$), benzo- diazepine (BZD), and beta-adrenergic receptors.

Olanzapine's high affinity binding to and antagonism of, muscarinic M_1, M_2, M_3, M_4, and M_5 receptors may explain its anticholinergic effects. Olanzapine also binds with high affinity to histamine H_1 and α_1-adrenergic receptors.

PHARMACOKINETICS

Olanzapine is well absorbed from the gastro-intestinal tract after oral doses but undergoes considerable first-pass metabolism. Peak plasma concentrations occur about 5 to 8 hours after oral doses and about 15 to 45 minutes after an intramuscular dose. Olanzapine is about 93% bound to plasma proteins. It is extensively metabolized in the liver, mainly by direct glucuronidation and by oxidation mediated through the cytochrome P450 isoenzymes CYP1A2, and, to a lesser extent, CYP2D6. The 2 major metabolites, 10-N-glucuronide and 4'-N-desmethyl olanzapine, appear to be inactive. About 57% of a dose is excreted in the urine, mainly as metabolites, and about 30% appears in the faeces. The mean plasma elimination half-life has been variously reported to be about 30 to 38 hours; half-lives tend to be longer in female than in male patients. Olanzapine is distributed into breast milk.

INDICATION

- Olanzapine is indicated for the treatment of schizophrenia.
- Olanzapine is effective in maintaining the clinical improvement during continuing therapy in patients who have shown initial treatment response.
- Olanzapine is indicated for short-term treatment of acute manic episode associated with Bipolar I Disorder.
- Olanzapine is indicated for preventing recurrence of manic, mixed or depressive episodes in Bipolar I Disorder.

CONTRAINDICATION

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

WARNINGS AND PRECAUTIONS

- Unsuitable for phenylketonurics.
- 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.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Discontinue olanzapine if DRESS is suspected.
- **Dementia-related psychosis and/or behavioural disturbances:** Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident.
- **Parkinson's disease:** The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended.
- **Neuroleptic Malignant Syndrome (NMS):** NMS is a potentially life-threatening condition associated with antipsychotic medicinal products. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are 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 phosphokinase,myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptom indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.
- **Hyperglycaemia and Diabetes Mellitus:** Hyperglycaemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics 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. Given this confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.
  Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
- **Lipid alterations:** Undesirable alterations in lipids have been observed in olanzapine-treated patients. Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic medicines, including olanzapine, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g., at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.
- **Anticholinergic activity:** Olanzapine demonstrated low incidence of anticholinergic activity. Caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions.
- **Hepatic function:** Transient, asymptomatic elevations of hepatic aminotransferases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised and follow-up organised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicines. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.
- **Neutropenia:** 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.
- **Discontinuation of treatment:** Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely when olanzapine is stopped abruptly.
- **QT interval:** Caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypomagnesaemia or hypokalaemia.
- **Thromboembolism:** Temporal association of olanzapine treatment and venous thromboembolism has been reported uncommonly. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism, all possible risk factors of VTE e.g., immobilisation of patients should be identified and preventive measures undertaken.
- **General CNS activity:** 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 antagonise the effects of direct and indirect dopamine agonists.
- **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. Seizures have been reported in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures was reported.
- **Tardive dyskinesia:** Olanzapine was associated with a 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 temporally deteriorate or even arise after discontinuation of treatment.
- **Postural hypotension:** Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. It is recommended that blood pressure is measured periodically in patients over 65 years.
- **Sudden cardiac death:** The event of sudden cardiac death has been reported in patients with olanzapine.
- **Paediatric population:** Olanzapine is not indicated for use in the treatment of children and adolescents. Various adverse reactions shown are weight gain, changes in metabolic parameters and increases in prolactin levels.
- **Phenylalanine:** Hovid Olanzapine Orodispersible Tablet contains aspartame, which is a source of phenylalanine. May be harmful for people with phenylketonuria.
- **Mannitol:** Hovid Olanzapine Orodispersible Tablet contains mannitol.
- Avoid alcoholic beverages.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

No studies on the effects on 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.

PREGNANCY AND LACTATION

Pregnancy

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 foetus.

Neonates exposed to antipsychotic drugs (including olanzapine) 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 on severity. While in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation.

Hovid Olanzapine Orodispersible Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

Olanzapine was excreted in breast milk. Patients should be advised not to breastfeed an infant if they are taking olanzapine.

DRUG INTERACTIONS

Interaction studies have only been performed in adults.

Potential interactions affecting olanzapine

Since olanzapine is metabolised 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.

Inhibition of CYP1A2

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.

Decreased 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.

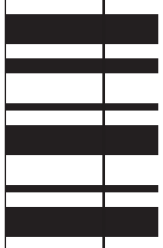
Fluoxetine (a CYP2D6 inhibitor), single doses of antacid (aluminium, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.

Potential for olanzapine to affect other medicinal products

Olanzapine may antagonise the effects of direct and indirect dopamine agonists. Olanzapine does not inhibit the main CYP450 isoenzymes *in vitro* (e.g., 1A2, 2D6, 2C9, 2C19, 3A4).

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 olanzapine.



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General CNS activity
Caution should be exercised in patients who consume alcohol or receive medicinal products that can cause central nervous system depression.The concomitant use of olanzapine with anti- Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended.

QTc interval
Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval.

MAIN SIDE / ADVERSE EFFECTS

Adult
The most frequently reported adverse reactions associated with the use of olanzapine were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels, glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia, dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases, rash, asthenia, fatigue, pyrexia, arthralgia, increased alkaline phosphatase, high gamma glutamyl- transferase, high uric acid, high creatine phosphokinase and oedema. Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea and vomiting have been reported when olanzapine is stopped abruptly.

Blood and the lymphatic system disorders
Common: Eosinophilia, Leukopenia, Neutropenia
Rare: Thrombocytopenia

Immune system disorders
Uncommon: Hypersensitivity

Metabolism and nutrition disorders
Very common: Weight gain
Common: Elevated cholesterol levels, Elevated glucose levels, Elevated triglyceride levels, Glucosuria, Increased appetite
Uncommon: Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases
Rare: Hypothermia

Nervous system disorders
Restless legs Syndrome
Very common: Somnolence
Common: Dizziness, Akathisia, Parkinsonism, Dyskinesia
Uncommon: Seizures where in most cases a history of seizures or risk factors for seizures were reported, Dystonia (including oculogyration), Tardive dyskinesia, Amnesia, Dysarthria
Rare: Neuroleptic malignant syndrome, Discontinuation symptoms

Cardiac disorders
Uncommon: Bradycardia, QTc prolongation
Rare: Ventricular tachycardia/fibrillation, sudden death

Vascular disorders
Very common: Orthostatic hypotension
Uncommon: Thromboembolism (including pulmonary embolism and deep vein thrombosis)

Respiratory, thoracic and mediastinal disorders
Sleep apnoea (A typical antipsychotic drugs, such as Olanzapine, have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, Hovid Olanzapine Orodispersible Tablets should prescribed with caution.
Uncommon: Epistaxis

Gastrointestinal disorders
Common: Mild, transient anticholinergic effects including constipation and dry mouth
Uncommon: Abdominal distension
Rare: Pancreatitis

Hepatobiliary disorders
Common: Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment
Rare: Hepatitis (including hepatocellular, cholestatic or mixed liver injury)

Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Photosensitivity reaction, Alopecia
Very Rare: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Musculoskeletal and connective tissue disorders
Common: Arthralgia
Rare: Rhabdomyolysis

Renal and urinary disorders
Urinary retention
Uncommon: Urinary incontinence, Urinary hesitation

Pregnancy, Puerperium and perinatal conditions
Not known: Drug withdrawal syndrome neonatal

Reproductive system and breast disorders
Common: Erectile dysfunction in males, Decreased libido in males and females
Uncommon: Amenorrhea, Breast enlargement, Galactorrhea in females, Gynaecomastia/breast enlargement in males
Rare: Priapism

General disorders and administration site conditions
Common: Asthenia, Fatigue, Oedema, Pyrexia

Investigations
Very common: Elevated plasma prolactin levels
Common: Increased alkaline phosphatase, High creatine phosphokinase, High gamma glutamyltransferase, High uric acid
Uncommon: Increased total bilirubin

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations
In elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions. Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

In patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly.

Valproate combination therapy with olanzapine resulted in an incidence of neutropenia; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase from baseline body weight occurred in patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase from baseline body weight in patients.

Paediatric population
Olanzapine is not indicated for the treatment of children and adolescent patients below 18 years.

The following summarises the adverse reactions reported with a greater frequency in adolescent patients (aged 13-17 years) than in adult patients.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders
Very common: Weight gain, elevated triglyceride levels, increased appetite
Common: Elevated cholesterol levels

Nervous system disorders
Very common: Sedation (including: hypersomnia, lethargy, somnolence)

Gastrointestinal disorders
Common: Dry mouth

Hepatobiliary disorders
Very common: Elevations of hepatic aminotransferases (ALT/AST)

Investigations
Very common: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels

OVERDOSAGE AND TREATMENT

Signs and symptoms
Very common symptoms in overdose 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, 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 approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of 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 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension 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.

DOSAGE AND ADMINISTRATION

Olanzapine orodispersible tablet has the same dosage and frequency of administration as olanzapine coated tablets. Olanzapine orodispersible tablets may be used as an alternative to olanzapine coated tablets.

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

Schizophrenia
The recommended starting dose for olanzapine is 10 mg/day.

Manic episode
The starting dose 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 is 10 mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose.

Olanzapine can be given without regard for meals, as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

Hovid Olanzapine Orodispersible Tablets should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice, milk, or coffee) immediately before administration.

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.

Smokers
The starting dose and dose range need not be routinely altered for non-smoking patient relative to smoking patient. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary.

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

Paediatric population
Olanzapine is not recommended for use in children and adolescents below 18 years. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in adolescent patients than in adult patients.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage: Store below 30°C. Protect from light and moisture.

Presentation/Packing: Blister pack of 3 x 10's.

Product Registration Holder: **HOVID Bhd.**
121, Jalan Tunku Abdul Rahman (Jalan Kuala Kangsar),
30010 Ipoh, Perak, Malaysia.
Manufactured by: Jubilant Generics Ltd.
Village Sikandarpur Bhainswal Roorkee-Dehradun Highway,
Bhagwanpur, Roorkee, District-Haridwar, Uttarakhand - 247661, India.

Information Date: October 2021

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