PharmaKoe

Product Information

Olancor

olanzapine film-coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each OLANCOR 5 mg & 10mg Film Coated Tablet contains 5 mg, & 10mg olanzapine respectively.

PHARMACEUTICAL FORM

OLANCOR FC TABLETS 10MG are white, round biconvex tablets with diameter 10.1mm±0.1mm and thickness 4.1mm±0.2mm.

OLANCOR FC TABLETS 5MG white, round biconvex tablets with diameter 8.1mm±0.1mm and thickness 3.1mm±0.2mm.

CLINICAL PARTICULARS

Therapeutic indications

Olanzapine is indicated for the acute and maintenance treatment of schizophrenia and other psychoses 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. Olanzapine also alleviates the secondary affective symptoms commonly associated with schizophrenia and related disorders.

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.

4.1.2 Further information on clinical trials

In a multinational, double-blind, comparative study of schizophrenia, schizoaffective, and related disorders which included 1,481 patients with varying degrees of associated depressive symptoms (baseline mean of 16.6 on the Montgomery-Asberg Depression Rating Scale), a prospective secondary analysis of baseline to endpoint mood score change demonstrated a statistically significant improvement (p=0.001) favouring olanzapine (-6.0) versus haloperidol (-3.1).

4.2. Posology and method of administration

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. (See Section 5.1)

Preventing recurrence in bipolar disorder: The recommended starting dose is 10mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

During treatment for both 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 intervals of not less than 24 hours. Olanzapine can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

Children: Olanzapine has not been studied in subjects under 18 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 factors 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 be routinely altered for female patients relative to male patients.

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

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.(See also Section 4.5, Interaction with Other Medicaments and Other Forms of Interaction, and Section 5.2, Pharmacokinetic properties)

4.3. Contraindications

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

4.4. Special warnings and special precautions for use

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. OLANCOR is not approved for the treatment of patients with dementia-related psychosis.

There is an increased prevalence of diabetes in patients with schizophrenia. As with some other antipsychotics, hyperglycaemia, diabetes, exacerbation of pre-existing diabetes, ketoacidosis, diabetic coma and death have been reported. Appropriate clinical monitoring is recommended in all patients, particularly in diabetic patients and in patients with risk factors for the development of diabetes (See 4.8 Undesirable Effects).

Assessment of 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. Given these 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 studied. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available. The available data are insufficient to provide reliable estimates of differences in hyperglycaemia-related adverse event risk among the marketed atypical antipsychotics.

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.

Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo controlled clinical trials (see section 4.8 Undesirable Effects). Appropriate clinical monitoring is recommended.

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.

Concomitant illnesses: While olanzapine demonstrated anticholinergic activity in vitro, experience during the clinical trials revealed a low incidence of related events. However, 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. In clinical trials, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo, and olanzapine was not more effective than placebo in the treatment of psychotic symptoms. In these trials, patients were initially required to be stable on the lowest effective dose of anti-Parkinsonian medications (dopamine agonist) and to remain on the same anti-Parkinsonian medications and dosages throughout the study. Olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.

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.

Lactose: OLANCOR Film coated tablets contain lactose.

Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen commonly, especially in early treatment. Rare post-marketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the post marketing period. Caution should be exercised 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 drugs. In the event of elevated ALT and/or AST during treatment, follow up should be organised and dose reduction should be considered. In cases where hepatitis has been diagnosed, olanzapine treatment should be discontinued.

As with other neuroleptic drugs, caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients with a history of drug-induced bone marrow depression/toxicity, in patients receiving medicines known to cause neutropenia, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Thirty two patients with clozapine-related neutropenia or agranulocytosis histories received olanzapine without decreases in baseline neutrophil counts. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

There are limited data on co-medication with lithium and valproate (see section 5.1). There are no clinical data available on olanzapine and carbamazepine co-therapy, however a pharmacokinetic study has been conducted (see section 4.5).

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially life-threatening condition associated with antipsychotic medication. 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 creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs, 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 were reported.

Tardive Dyskinesia: In comparator studies of one year or less duration, 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 drug discontinuation should be considered. These symptoms can temporally 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 drugs 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.

In clinical trials, olanzapine was not associated with a persistent increase in absolute QT intervals. Only 8 of 1,685 subjects had increased QTc interval on multiple occasions. However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with drugs known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Safety Experience in Elderly Patients with Dementia–Related Psychosis: In elderly patients with dementia-related psychosis, the efficacy of olanzapine has not been established. In placebo controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine- treated patients was significantly greater than placebo-treated patients (3.5% vs. 1.5%, respectively). Risk factors that may predispose this patient population to increased mortality when treated with olanzapine include age ≥80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g., pneumonia, with or without aspiration).

Cerebrovascular Adverse Events (CVAE), Including Stroke, in Elderly Patients with Dementia: Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo controlled studies, there was a higher incidence of CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All patients who experienced a cerebrovascular event had pre-existing risk factors known to be associated with an increased risk for a CVAE (e.g., history of previous CVAE or transient ischemic attack, hypertension, cigarette smoking) and presented with concurrent medical conditions and/or concomitant medications having a temporal association with CVAE. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

4.5. Interaction with other medicinal products and other forms of interaction

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

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. 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 (See section 4.2, Posology and method of administration).

Inhibition of CYP1A2: Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine Cmax following fluvoxamine was 54 % in female non-smokers and 77 % male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin or ketoconazole. 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). 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 antidepressant (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 olanzapine.

4.6. 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, this drug should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Spontaneous reports have been very rarely received on tremor, hypertonia, lethargy and sleepiness, in infants born to mothers who had used olanzapine during the 3rd trimester.

Lactation: In a study in lactating, 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 breast feed an infant if they are taking olanzapine.

4.7. Effects on ability to drive and use machines

Because olanzapine may cause somnolence, patients should be cautioned about operating hazardous machinery, including motor vehicles.

4.8. Undesirable effects

Adults

In clinical trials, mean weight gain was greater in patients treated with olanzapine than with placebo. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories.
In long-term studies (at least 48 weeks), both the magnitude of weight gain and the proportion of olanzapine-treated patients who had clinically significant weight gain were greater than in short-term studies. The percentage of patients who gained ≥25% of their baseline body weight with long-term exposure was very common (≥10%).

In clinical trials (up to 52 weeks) olanzapine was associated with a greater mean change in glucose relative to placebo.

The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (including those patients diagnosed with diabetes mellitus or who met criteria suggestive of hyperglycaemia), and these patients had a greater increase in HbA1c compared to placebo.

The proportion of patients who had a change in glucose level from normal or borderline at baseline to high increased over time. In an analysis of patients who completed 9-12 months of olanzapine therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

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 contributing 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% to 10%). During treatment with olanzapine in combination with lithium or divalproex, an increase of >7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks).

In clinical trials of up to 12 weeks in duration, olanzapine-treated patients had a greater mean increase in fasting total cholesterol, LDL cholesterol, and triglycerides, compared to placebo treated patients

Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline.

For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine- treated patients and placebo-treated patients.

The proportion of patients who had changes in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low, was greater in long-term studies (at least 48 weeks) as compared with short-term studies. In an analysis of patients who completed 12 months of therapy, the mean non-fasting total cholesterol did not increase further after approx-

imately 4-6 months.

Undesirable Effects for Special Populations: Very common (>10%) undesirable effects associated with the use of olanzapine in clinical trials with elderly patients with dementia-related psychosis were abnormal gait and falls. Common (<10% and >1%) undesirable effects associated with the use of olanzapine in elderly patients with dementia-related psychosis were urinary incontinence and pneumonia. In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology was reported very commonly and more frequently than with placebo. Also, hallucinations were reported very commonly and more frequently than with placebo. In these trials, patients were required to be stable on the lowest effective dose of anti-Parkinsonian

medications (dopamine agonist) prior to the beginning of the study and to remain on the same anti- Parkinsonian medications and dosages throughout the study. Olanzapine was started at 2.5 mg/day and titrated up to a maximum of 15 mg/day based on investigator judgement.

The following table of undesirable effects is 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 (see note 3 and 4 below), Weight gain ≥7% of baseline body weight (see note 5) *Common (1-10%):* Increased appetite. Elevated glucose levels (see note 1 below). Fatigue (see note 3 below), Weight gain ≥15% of baseline body weight (see note 6)
Nervous system disorders *Very common (>10%):* Somnolence. Abnormal gait has been observed in clinical trial patients with Alzheimer's disease. Worsening of Parkinsonian symptomatology and hallucinations were reported more frequently than with placebo in patients with Parkinson's disease. *Common (1-10%):* Dizziness (see note 3 below), akathisia. (See also note 2 below).
Cardiac disorders *Uncommon (0.1-1%):* Bradycardia with or without hypotension or syncope
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 (see also Section 4.4, Special warnings and special precautions for use).
Skin and subcutaneous tissue disorders *Uncommon (0.1-1%):* Photosensitivity reaction. Frequency Unknown: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
General disorders and administration site conditions *Common (1-10%):* Asthenia, oedema.
Investigations *Very common (>10%):* Elevated plasma prolactin levels (see note 3 and 4 below), 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. Fasting borderline to high total cholesterol (≥ 200mg/dL and <240 mg/dL to ≥240mg/dL). Fasting borderline to high triglycerides (≥150 mg/dL and <200 mg/dL to ≥200mg/dL. Fasting borderline to high glucose (≥100mg/dL and <126 mg/dL to ≥126 mg/dL) Fasting borderline to high LDL cholesterol (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL *Common (1-10%):* Fasting normal to high total cholesterol (<200mg/dL to ≥240mg/dL)4,. Fasting normal to high triglycerides (<150mg/dL to ≥200mg/dL)4. Fasting normal to high glucose (<100 mg/dL to ≥126mg/dL. Glycosuria. *Uncommon (0.1-1%):* High creatine phosphokinase.

[1]In clinical trials with olanzapine in over 5000 patients with baseline non-fasting glucose levels ≤ 7.8 mmol/l, the incidence of non-fasting plasma glucose levels ≥ 11 mmol/l (suggestive of diabetes) was 1.0%, compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels ≥ 8.9 mmol/l but < 11

mmol/l (suggestive of hyperglycaemia) was 2.0%, compared to 1.6% with placebo. Hyperglycaemia is also reported as a Rare (0.01-0.1%) spontaneous event.

[2]In clinical trials, the incidence of parkinsonism and dystonia in olanzapine-treated patients was not significantly different from placebo. Olanzapine-treated patients had a lower incidence of parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

[3]Statistically significant differences among 3 dose groups were observed in a single 8-week randomized, double-blind, fixed-dose study comparing 10, 20 and 40 mg/day of olanzapine in patients with schizophrenia or schizoaffective disorder.

[4]Statistically significant differences among dose groups were observed in a 24-week fixed-dose study comparing 150mg/2wk, 405mg/4wk, and 300mg/2wk of olanzapine pamoate in patients with schizophrenia. For triglycerides, this difference among doses was observed for fasting normal levels which increased to high levels (<150mg/dL to ≥200 mg/dL).

[5]Median duration of exposure 8 weeks.

[6]Median duration of exposure 12 weeks.

The following table of undesirable effects is based on post-marketing spontaneous reports.

Blood and lymphatic system disorders *Rare (0.01-0.1%):* Leukopenia including neutropenia *Very rare (<0.01%):* Thrombocytopenia. Neutropenia.
Cardiovascular *Very rare (<0.01%):* Venous thromboembolism including pulmonary embolism and deep vein thrombosis
Immune system disorders *Very rare (<0.01%):* Allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritis or urticaria).
Metabolism and nutrition disorders *Very rare (<0.01%):* Hypertriglyceridaemia7. Hypercholesterolemia7. Rare (0.01-0.1%): Hyperglycaemia
Musculoskeletal System *Very rare (<0.01%):* Rhabdomyolosis
Nervous system disorders *Rare (0.01-0.1%):* Seizures have been reported to occur rarely in patients treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported. *Very rare (<0.01%):* Cases reported as Neuroleptic Malignant Syndrome (NMS) have been received in association with olanzapine. (See also Section 4.4, Special warnings and special precautions for use). Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely when olanzapine is stopped abruptly.
Gastrointestinal disorders *Very rare (<0.01%):* Pancreatitis.
Hepato-biliary disorders *Rare (0.01 - 0.1%):* Hepatitis. Very rare (<0.01%): Jaundice
Skin and subcutaneous tissue disorders *Rare (0.01-0.1%):* Rash. *Very Rare (< 0.01%):* Alopecia
Renal and urinary disorders *Very rare (<0.01%):* Urinary hesitation.
Reproductive system and breast disorders *Very rare (<0.01%):* Priapism
Psychiatric disorders *Not known (cannot be estimated from the data available):* Somnambulism (sleep walking) and Sleep-related eating disorder
Investigations . *Very rare (<0.01%):* Increased alkaline phosphatase. Increased total bilirubin.

[7]Random cholesterol level of ≥240mg/dL and random triglyceride levels of ≥1000mg/dL have been very rarely reported.

Post-Market Adverse Drug Reactions:
Based on post-marketing reports, atypical antipsychotic drugs, including 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, olanzapine should be prescribed with caution.

4.9. Overdose

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, hyperten sion or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450mg but survival has also been reported following acute overdose of 1,500mg.

Management of Overdose

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 char coal 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Olanzapine is an antipsychotic, ATC code N05A H03.

Olanzapine is an antipsychotic agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5 HT2A/2C, 5 HT3, 5 HT6; dopamine D1, D2, D3, D4, D5; cholinergic musca rinic receptors m1-m5; α1 adrenergic; and histamine H1 receptors. Animal behavioral studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consis

tent with the receptor binding profile. Olanzapine demonstrated a greater in-vitro affinity for serotonin 5HT2 than dopamine D2 receptors and greater 5 HT2 than D2 activity in vivo, models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a condi tioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an "anxiolytic" test.

In a single oral dose (10 mg) Positron Emission tomography (PET) study in healthy volunteers, olanzapine produced a higher 5 HT2A than dopamine D2 receptor occupancy. In addition, a SPECT imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

In two of two placebo and two of three comparator controlled trials with over 2,900 schizophrenic patients presenting with both positive and negative symptoms, olanzapine was associated with statistically significantly greater improvements in negative as well as positive symptoms.

In patients with a manic or mixed episode of bipolar disorder, olanzapine demonstrated superior efficacy to placebo and valproate semisodium (divalproex) in reduction of manic symptoms over 3 weeks. Manic symptoms have been shown to be reduced by olanzapine as early as day 2. Olanzapine also demonstrated comparable efficacy results to haloperidol in terms of the proportion of patients in symptomatic remission from mania and depression at 6 and 12 weeks. In a co-therapy study of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of olanzapine 10 mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

In a 12-month recurrence prevention study in manic episode patients who achieved remission on olanzapine and were then randomised to olanzapine or placebo, olanzapine demonstrated statistically significant superiority over placebo on the primary endpoint of bipolar recurrence. Olanzapine also showed a statistically significant advantage over placebo in terms of preventing either recurrence into mania or recurrence into depression, although a greater advantage was seen in preventing recurrence into mania.

In a second 12-month recurrence prevention study in manic episode patients who achieved remission with a combination of olanzapine and lithium and were then randomised to olanzapine or lithium alone, olanzapine was statistically non-inferior to lithium on the primary endpoint of bipolar recurrence (olanzapine 30.0%, lithium 38.8%). Olanzapine showed a statistically significant advantage over lithium on recurrence into mania and was not statistically significantly different from lithium on recurrence into depression.

In an 18-month co-therapy study in manic or mixed episode patients stabilised with olanzapine plus a mood stabiliser (lithium or valproate), long-term olanzapine co-therapy with lithium or valporate was not statistically significantly superior to lithium or valproate alone in delaying bipolar recurrence, defined according to syndromic (diagnostic) criteria.

5.2. Pharmacokinetic properties

Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food. Absolute oral bioavailability relative to intravenous administration has not been determined

Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which 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. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hr) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia > 65 years of age, dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

In female versus male subjects the mean elimination half-life was somewhat prolonged (36.7 versus 32.3 hrs) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20 mg) demonstrated a comparable safety profile in female (n=467) as in male patients (n=869).

In renally impaired patients (creatinine clearance < 10 ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hr) or drug clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57 % of radiolabeled olanzapine appeared in urine, principally as metabolites.

In smoking subjects with mild hepatic dysfunction, mean elimination half-life (39.3 hr) was prolonged and clearance (18.0 l/hr) was reduced analogous to non-smoking healthy subjects (48.8 hr and 14.1 l/hr, respectively).

In non-smoking versus smoking subjects (males and females) the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr).

The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations.

The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/mL. Olanzapine is bound predominantly to albumin and α1-acid glycoprotein.

5.3. Preclinical safety data

Acute (Single-dose) toxicity

Signs of oral toxicity in rodents were characteristic of potent neuroleptic compounds: hypoactivity, coma, tremors, clonic convulsions, salivation, and depressed weight gain. The median lethal doses were approximately 210 (mice) and 175 (rats) mg/kg. Dogs tolerated single oral doses up to 100 mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, labored respiration, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and, at higher doses, semi-consciousness.

Repeated-dose toxicity

In studies up to 3 months duration in mice and up to 1 year in rats and dogs, the predominant effects were CNS depression, anticholinergic effects, and peripheral haematological disorders. Tolerance developed to the CNS depression. Growth parameters were decreased at high doses. Reversible effects consistent with elevated prolactin in rats included decreased weights of ovaries and uterus and morphologic changes in vaginal epithelium and in mammary gland.

Haematologic toxicity: Effects on haematology parameters were found in each species, including dose- related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [AUC] is 12- to 15-fold greater than that of a man given a 12-mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

Reproductive toxicity

Olanzapine had no teratogenic effects. Sedation affected mating performance of male rats. Estrous cycles were affected at doses of 1.1 mg/kg (3 times the maximum human dose) and reproduction parameters were influenced in rats given 3 mg/kg (9 times the maximum human dose). In the offspring of rats given olanzapine, delays in fetal development and transient decreases in offspring activity levels were seen.

Mutagenicity

Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and in vitro and in vivo mammalian tests.

Carcinogenicity

Based on the results of studies in mice and rats, it was concluded that olanzapine is not carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 Excipients

OLANCOR Film Coated Tablet

Lactose monohydrate 150 mesh, Microcrystalline cellulose, Crospovidone, Hydroxypropylcellulose, Talc, Magnesium stearate, Opadry AMB White OY-B-28920 (Polyvinyl Alcohol - Part hydrolyzed, Titanium Dioxide, Talc, Lecithin (Soya), Xanthan Gum)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Expiry date is indicated on the packaging.

6.4 Special precautions for storage

This product should be stored in a dry place at or below 30ºC.

6.5 Nature and contents of container

Blister packs of 28's (4x7's) and 1000's (100x10's)

For further information, please consult your physician or pharmacist.

OLANCOR FC Tablets

Manufactured For:
PharmaKoe pte. Ltd.
26 Kallang Place #05-17,
Singapore 339157

Manufactured by:
Pharmathen S.A.
Dervenakion 6, Pallini Attiki ,
15351, GreeceAnd

OMAN PHARMACEUTICAL PRODUCTS CO. LLC
Raysut Industrial Estate Plot 101, Salalah, Sultanate of Oman

Date of Revision: 04-2023

LT-0013/02