PROPOSED PACKAGE INSERT FOR OLEXAR 2.5 (TABLETS), OLEXAR 5 (TABLETS), OLEXAR 10 (TABLETS)

SCHEDULING STATUS:
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PROPRIETARY NAME (AND DOSAGE FORM):
OLEXAR 2.5 (TABLETS)
OLEXAR 5 (TABLETS)
OLEXAR 10 (TABLETS)

COMPOSITION:

OLEXAR 2.5 :	Each tablet contains 2.5 mg olanzapine.
OLEXAR 5 :	Each tablet contains 5 mg olanzapine.
OLEXAR 10 :	Each tablet contains 10 mg olanzapine.

PHARMACOLOGICAL CLASSIFICATION:
A 2.6.5 Tranquillisers – miscellaneous structures.

PHARMACOLOGICAL ACTION: (*Ref: 1, 3, 5, 8, 9, 10*)

Pharmacodynamic properties:
Olanzapine is a psychotropic agent which belongs to the thienobenzodiazepine class. It is an antipsychotic agent with selective mono-aminergic antagonist activity due to high affinity for the following receptors: serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$; dopamine $D_{1\text{-}5}$; cholinergic muscarinic $M_{1\text{-}5}$; α_1-adrenergic; and histamine H_1 receptors. Studies also demonstrate that olanzapine selectively interacts with the mesolimbic system without significantly interacting with the extrapyramidal system (striatal pathways involved in motor function). Olanzapine reduces a conditioned avoidance response, a test predictive of antipsychotic activity, at doses below those required to produce catalepsy, a test predictive of motor side-effects. Olanzapine increases responding in an "anxiolytic" test. In a single dose (10 mg) PET study in healthy volunteers, olanzapine produced higher $5HT_{2A}$ than dopamine D_2 receptor occupancy.

Olanzapine's antagonism of muscarinic receptors ($M_1 - _5$) may explain its anticholinergic effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this medicine. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this medicine.

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. Olanzapine undergoes extensive first pass metabolism, with approximately 40 % of the dose metabolized before reaching the systemic circulation. Olanzapine displays linear kinetics over the clinical dosing range. Once daily olanzapine leads to steady-state concentrations in about one week (which is about twice the concentrations after single doses).

Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucoronide, which does not pass the blood brain barrier. Other metabolites include the N-desmethyl and 2-hydroxymethyl metabolites, neither of which have significant *in vivo* pharmacological activity. The predominant pharmacological activity is from the parent compound. After oral administration, the elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender:

	< 65 years	**≥ 65 years**
Men	29 hours	49 hours
Women	39 hours	55 hours

In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1,5 times greater in the elderly (≥ 65 years) than in the non-elderly subjects (< 65 years). Caution should be exercised in dosing the elderly, especially if there are any factors that might additively influence medicine metabolism and / or pharmacodynamic sensitivity.

Plasma clearance of olanzapine is higher in smokers.

The combined effects of age, smoking and gender could lead to substantial pharmacokinetic differences in different population groups. The clearance in young smoking males, for example, may be 3 times higher than that in elderly non-smoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine.

Olanzapine is excreted via the renal (± 57 %) and faecal route (± 30 %). Only 7 % of the dose of olanzapine was recovered in the urine as the unchanged drug, indicating extensive metabolism.

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.

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 α_1-acid-glycoprotein.

INDICATIONS: *(Ref: 1, 3, 4, 5, 6, 7, 8, 9, 10)*
OLEXAR is indicated for the management of the manifestations of psychotic disorders (including schizophrenia and bipolar mania).

Schizophrenia:
The antipsychotic efficacy of olanzapine was established in short-term (6 week) controlled trials of schizophrenic in-patients in the treatment of positive symptoms (such as delusions, hallucinations, disordered thinking, hostility and suspiciousness) and negative symptoms (such as blunted effect, emotional and social withdrawal, poverty of speech).

The effectiveness of olanzapine at maintaining a treatment response in schizophrenic patients, followed for a period of up to 8 months, has been demonstrated in a placebo-controlled trial involving 326 outpatients. It is recommended that responding patients be continued on **OLEXAR**, at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Bipolar mania:
OLEXAR is also indicated for the short-term treatment of acute manic episodes associated with Bipolar I Disorder (alternating manic and major depressive episodes).

The effectiveness of olanzapine was established in placebo-controlled trials in patients with confirmed Bipolar I Disorder who displayed acute manic or mixed episodes with or without psychotic features. The efficacy of olanzapine for long-term use (> 4 weeks), and for prophylaxis of mania, has not been systemically evaluated in controlled clinical trials. Should a physician elect to use **OLEXAR**, for this indication, for extended periods, the potential risks and benefits for each individual should be periodically re-evaluated.

CONTRA-INDICATIONS: *(Ref: 3, 6, 7, 8, 9, 10)*
OLEXAR is contra-indicated in patients with known hypersensitivity to any ingredient of the product. It is also contra-indicated in patients with a known risk for narrow-angle glaucoma.

Use in pregnancy and lactation:
Safety of olanzapine during pregnancy and lactation has not been established.

In reproduction studies in rats at doses of up to 18 mg / kg /day and in rabbits at doses of up to 30 mg / kg / day (9 and 30 times the maximum recommended human daily dose on a mg / m^2 basis, respectively), no evidence of teratogenicity was observed.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Because animal reproduction studies are not always predictive of human response, this medicine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Paediatric use:
Safety and effectiveness in patients under 18 years of age have not been established.

WARNINGS: *(Ref: 1, 3, 6, 7, 8, 9, 10)*
Hyperprolactinaemia: Olanzapine elevates prolactin levels and a modest elevation persists during chronic administration. In studies conducted in mice and rats, compounds which increase prolactin release, have led to an increase in mammary gland neoplasia in these animals. However, neither epidemiological or clinical studies have shown an association between chronic administration of this class of drug and tumorigenesis in humans; the relevance of these animal findings to human risk is considered too limited to be conclusive.

Neuroleptic malignant syndrome (NMS): NMS, a potentially life-threatening condition, has been associated with antipsychotic medicines, including olanzapine in rare cases. Clinically, patients with NMS present with altered mental status, evidence of autonomic instability (cardiac dysrhythmia, diaphoresis, irregular pulse or blood pressure and tachycardia), hyperpyrexia and muscle rigidity. These patients can also present with raised creatinine phosphokinase, myoglobinuria (due to rhabdomyolysis) and acute renal failure. Should a patient present with clinical manifestations indicative of NMS, or unexplained high fever without other signs and symptoms of NMS, all antipsychotic medicines, including olanzapine, must be discontinued. Symptomatic treatment, general supportive measures and medical monitoring should also be instituted. If a patient requires antipsychotic treatment again after a previous episode of NMS, it should be considered carefully, since recurrences of NMS have been reported. Reintroduction requires careful monitoring.

Seizures: **OLEXAR** should be used cautiously in patients who have a history of seizures or have conditions which may reduce seizure threshold, e.g. Alzheimer's dementia. Seizures have been reported infrequently in patients on olanzapine.

Tardive dyskinesia: Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements. Olanzapine was associated with a low incidence of treatment emergent dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on **OLEXAR**, a dose reduction or discontinuation of treatment should be considered. However, some patients may benefit from continued treatment with **OLEXAR** despite the presence of the syndrome. The risk of tardive dyskinesia increases with duration of exposure to olanzapine (there is also increased prevalence in the elderly, especially elderly women). Symptoms can deteriorate temporarily or even arise after discontinuation of treatment.

Hepatic impairment: Caution should be exercised in patients with elevated ALT and / or AST, in patients with clinical manifestations of hepatic impairment, in patients with conditions associated with limited hepatic functional reserve, and in patients who are on potentially hepatotoxic medicines. Periodic assessment of transaminases is recommended in patients with any of the above. A 5 mg starting dose should be considered in patients with moderate hepatic impairment.

DOSAGE AND DIRECTIONS FOR USE: (*Ref: 1, 3, 7, 8, 9, 10*)

Schizophrenia:
In order to evaluate efficacy and guard against side-effects, dosage increases should not be considered at intervals shorter than one week.

OLEXAR should be administered on a once-a-day schedule without regard to meals, generally beginning with an initial dose of 5 to 10 mg / day, 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 one week, since steady state for olanzapine would not be achieved for approximately one week. When dosage adjustments are necessary, dose increments / decrements of 5 mg once daily are recommended.

The safety of doses above 20 mg / day has not been evaluated in clinical trials.

Special populations: The starting dose and dose range need not be routinely altered for female patients relative to male patients, for non-smokers relative to smokers, for elderly patients and for patients with renal impairment (see "Pharmacological action"). However, when a combination of these factors are present, which may result in slower metabolism (e.g. a non-smoking, elderly, female patient), consideration should be given to reducing the starting dose to 5 mg daily. Dose escalation, when necessary, should be conservative in such patients.

A starting dose of 5 mg once daily should also be considered in patients who are debilitated, who are older than 65 years, who have a predisposition to hypotensive reactions, or who have significant hepatic impairment.

Biopolar mania:
Starting dosage: 10 to 15 mg once daily, without regard to meals.

Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours. When these are necessary, dose increments / decrements of 5 mg once daily are recommended.

The safety of doses above 20 mg/day has not been evaluated in clinical studies.

Special populations: See "Special populations" under "Dosage and Directions for Use: Schizophrenia".

SIDE-EFFECTS AND SPECIAL PRECAUTIONS: (*Ref: 1, 3, 4, 5, 6, 7, 8, 9, 10*)

Side-effects:
The following adverse reactions have been reported in association with olanzapine treatment:

General: *Frequent (1-10%)*: asthenia, fever, accidental injury, dental pain, chest pain, flu syndrome, and intentional injury; *Infrequent (0,1 – 1 %)*: enlarged abdomen, chills, facial oedema, malaise, moniliasis, neck pain, neck rigidity, pelvic pain and photosensitivity reaction; *Rare (0,01 – 0,1 %)*: hangover effect.

Neuropsychiatric: *Very common (> 10 %)*: somnolence; *Frequent*: dizziness, personality disorder, akathisia, tremor, insomnia, abnormal gait, hypertonia, articulation impairment, abnormal dreams, emotional lability, euphoria, decreased libido, paresthesia and schizophrenic reaction; *Infrequent*: alcohol misuse, withdrawal syndrome, amnesia, vertigo, tobacco misuse, antisocial behaviour, ataxia, CNS stimulation, tardive dyskinesia, shuttering, stupor, stimulant misuse, cogwheel rigidity, coma, delirium, depersonalization, dysarthria, somatization, phobias, obsessive compulsive symptoms, increased libido, facial paralysis, incoordination, hypesthesia, hypotonia and hypokinesia; *Rare*: seizures (see "Warnings"), subarachnoid hemorrhage, akinesia, circumoral paresthesia, paralysis, nystagmus, neuropathy, encephalopathy and neuralgia; *Very rare (< 0,01 %)*: neuroleptic malignant syndrome (NMS) – see "Warnings".

Respiratory: *Frequent*: increased cough, pharyngitis, rhinitis and dyspnoea; *Infrequent*: voice alteration, apnoea, aspiration pneumonia, pneumonia, laryngitis, hyperventilation, asthma, atelectasis, epistaxis and hemoptysis; *Rare*: hiccup, stridor, lung oedema, hypoventilation and hypoxia.

Cardiovascular: *Frequent*: postural hypotension, hypertension, and tachycardia; *Infrequent*: bradycardia, with or without hypotension or syncope, ventricular extrasystoles, vasodilation, cerebrovascular accident, heart failure, cardiac arrest, palpitations, pallor, migraine and hemorrhage; *Rare*: pulmonary embolus, arteritis, and atrial fibrillation.

Gastro-intestinal: *Frequent*: constipation, dry mouth, dyspepsia, increased appetite, vomiting, thirst, and increased salivation; *Infrequent*: tooth caries, dysphagia, eructation, tongue oedema, stomatitis, rectal hemorrhage, faecal impaction, faecal incontinence, flatulence, gastritis, periodontal abscess, oral moniliasis, nausea, mouth ulcers, melena, gastroenteritis, and gingivitis; *Rare*: tongue discoloration, aphthous stomatitis, enteritis, intestinal obstruction, ileus, glossitis, esophageal ulcer and esophagitis.

Hepato-biliary: *Frequent*: transient, asymptomatic elevations of hepatic transaminases; *Rare*: hepatitis, liver fatty deposits, increased CPK and GGT.

Metabolic / Nutritional: *Very common*: weight gain, and elevated plasma prolactin levels (without associated clinical manifestations); *Frequent*: elevated glucose levels, and peripheral oedema; *Infrequent*: water intoxication, diabetes mellitus, acidosis, increased alkaline phosphatase, hyponatremia, hypokalemia, hypoglycemia, hyperbilirubinemia, dehydration, hypercholesterolemia, hyperlipemia and hyperuricemia; *Rare*: diabetic acidosis, goiter, ketosis, gout, hyperkalemia, hypernatremia, hypoproteinemia, and albuminuria.

Musculoskeletal: *Frequent*: back pain, extremity pain, joint pain, joint stiffness and twitching; *Infrequent*: myasthenia, arthritis, arthrosis, bursitis and leg cramps; *Rare*: osteoporosis, bone pain and myopathy.

Dermatological: *Frequent*: sweating; *Infrequent*: vesicobullous rash, alopecia, contact dermatitis, skin ulcer, seborrhoea, pruritus, dry skin, eczema, and maculopapular rash; *Rare*: pustular rash, hirsutism, urticaria and skin discoloration.

Special senses: *Frequent*: amblyopia, and conjunctivitis; *Infrequent*: accommodation abnormalities, ocular muscle abnormality, eye pain, eye inflammation, eye hemorrhage, dry eyes, diplopia, corneal lesion, cataract, blepharitis, deafness, ear pain, tinnitus and taste perversion; *Rare*: keratoconjunctivitis, pigment deposits lens, miosis, mydriasis and macular hypopigmentation.

Urogenital: *Frequent*: urinary tract infections, urinary incontinence, hematuria, amenorrhoea, metrorrhagia and vaginitis; *Infrequent*: abnormal ejaculation, impotence, breast pain, female lactation, cystitis, dysuria, polyuria, pyuria, urinary frequency, urinary retention, decreased menstruation, increased menstruation, premenstrual syndrome, enlarged uterine fibroids and vaginal hemorrhage; *Rare*: gynecomastia, mastitis, oliguria, urinary urgency and priapism.

Haematological/Lymphatic: *Frequent*: ecchymosis, eosinophilia, and leukopenia; *Infrequent*: lymphadenopathy, anemia, leucocytosis, thrombocythemia, and thrombocytopenia; *Rare*: normocytic anemia.

Other events observed in patients treated with olanzapine in settings other than placebo-controlled clinical trials include a single case of exacerbation of pre-existing intracranial hypertension.

In clinical trials, there were no data to suggest olanzapine adversely affected bone marrow function, even in patients with a history of medicine-associated neutropenia or leucopenia.

Special precautions:

Concomitant illnesses: Clinical experience with olanzapine in patients with concomitant illness is limited. As olanzapine demonstrated anticholinergic activity *in vitro*, caution is advised when prescribing for patients with symptomatic prostatic enlargement, narrow-angle glaucoma or paralytic ileus and related conditions.

OLEXAR has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from pre-marketing clinical studies. Because of the risk of orthostatic hypotension with **OLEXAR**, caution should be observed in cardiac patients. As with other psychotropic medicines, olanzapine should be used with caution in elderly patients with dementia and / or Parkinson's disease.

Renal impairment: See "Pharmacokinetic properties".

Hepatic impairment: See "Warnings"

Orthostatic hypotension: Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and sometimes syncope, especially during the initial dose-titration period. Olanzapine should be used with caution in patients with conditions which predispose to hypotension (dehydration, hypovolemia and those on antihypertensive medication), patients with known cardiovascular disease (e.g. previous MI, heart failure or conduction abnormalities) and patients with cerebrovascular disease. The risk of hypotension may be minimized by starting with 5 mg once daily and a more gradual titration to the target dose, especially if hypotension occurs.

Potential for cognitive and motor impairment: Somnolence is a commonly reported dose-related adverse event associated with olanzapine. This may lead to impaired judgement, thinking or motor skills and patients must be cautioned about operating machinery, including automobiles, until they are reasonably certain that **OLEXAR** does not affect them adversely.

Temperature regulation: Antipsychotic drugs have been associated with the inability to reduce core body temperature in certain instances. Caution should be exercised when olanzapine is prescribed to patients who may experience elevation in body temperature, e.g. exposure to extreme heat, strenuous exercise, dehydration, or concomitant anticholinergic medication.

Dysphagia / Aspiration pneumonia: Esophageal dysmotility and aspiration have been associated with antipsychotic drugs, including olanzapine. Aspiration pneumonia is also commonly associated with Alzheimer's disease. Olanzapine should, therefore, be used with caution in patients at risk for aspiration pneumonia.

Suicide: The risk of suicide is inherent in schizophrenia and bipolar disorders. High-risk patients should therefore be closely supervised, and the smallest quantity of tablets, consistent with good patient management, should be prescribed, to reduce the risk of overdose.

Hyperglycemia: Due to rare cases of hyperglycemia or exacerbations of pre-existing diabetes (sometimes with keto-acidosis or coma), diabetic patients and patients at risk for development of diabetes should be monitored closely.

Haematology: Caution should be exercised when administering olanzapine to patients with the following conditions:

- leucopenia and / or neutropenia due to any reason,
- a positive history of drug-induced bone marrow depression or toxicity,
- bone marrow depression due to chemotherapy, radiotherapy or concomitant illness,
- myeloproliferative disease or hypereosinophilic conditions.

INTERACTIONS: (*Ref: 1, 3, 4, 5, 6, 7, 8, 9, 10*)
Caution should be exercised when **OLEXAR** is taken in combination with other centrally acting agents and alcohol. As it exhibits *in vitro* dopamine antagonism, **OLEXAR** may antagonize the effects of levodopa and dopamine agonists. Because of the potential for inducing hypotension, **OLEXAR** may enhance the effects of certain antihypertensive agents.

Potential interactions affecting OLEXAR: Since olanzapine is metabolized by CYP1A2, substances that induce or inhibit this iso-enzyme can affect the pharmacokinetics of olanzapine.

Inducers, such as rifampicin and omeprazole, may increase olanzapine clearance. Smoking and carbamazepine may also induce metabolism of olanzapine. Although the clinical consequences are likely to be limited, the olanzapine dose may need to be increased, if necessary.

Fluvoxamine, a specific CYP1A2 inhibitor, decreases the clearance of olanzapine significantly. Lower doses of olanzapine should be considered in patients on fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin or ketoconazole.

Activated charcoal reduces oral bio-availability of olanzapine by 50 – 60 %.

Single doses of cimetidine and antacids (aluminium- and / or magnesium – containing), as well as ethanol, fluoxetine, valproate and warfarin do not affect the pharmacokinetics of olanzapine significantly.

Potential for OLEXAR to affect other medicines: In clinical trials with single doses of olanzapine, no inhibition of the metabolism of imipramine / desipramine, warfarin, or diazepam was evident. Olanzapine showed no interaction when co-administered with lithium, biperiden, ethanol, theophylline or valproate. Also, in *in vitro* studies with human microsomes, olanzapine showed little potential to inhibit cytochromes P450-CYP1A2, -CYP2C9, -CYP2C19, -CYP2D6, and –CYP3A4. Given the extensive clinical and *in vitro* studies, **OLEXAR** would not be expected to interfere with the metabolism of most medicines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT: (*Ref: 3, 8, 9, 10*)

Symptoms:
Experience with olanzapine in overdosage is limited. The predicted symptoms would reflect an exaggeration of the agent's known pharmacological action and side-effects.

Symptoms that have been reported very commonly (> 10 %) after an overdosage, include agitation / aggression, tachycardia, dysarthria, various extrapyramidal symptoms and reduced levels of consciousness varying from sedation to coma. Other potentially medically serious events which have been reported less commonly, included respiratory

depression, aspiration, cardiopulmonary arrest, hypertension or hypotension, cardiac arrhythmias, delirium, convulsions, coma and possible neuroleptic malignant syndrome.

Treatment:
The possibility of multiple medicine involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose, may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine, therefore, appropriate symptomatic and supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and / or sympathomimetic agents. (Do not use epinephrine, dopamine or other sympathomimetics with ß-agonist activity, since ß stimulation may worsen hypotension in the setting of olanzapine-induced α blockade.) Close medical supervision and monitoring should continue until the patient recovers.

IDENTIFICATION:

OLEXAR 2.5:	Dark yellow coloured, circular, film coated, biconvex tablets with central breakline on one side and "2.5" embossed on the other side.
OLEXAR 5:	Light pink coloured, circular, film coated, biconvex tablets with central breakline on one side and "5" embossed on the other side.
OLEXAR 10:	White coloured, circular, film coated, biconvex tablets with central breakline on one side and "10" embossed on the other side.

PRESENTATION:
OLEXAR tablets are supplied in aluminium blister strips of 10 tablets, packed in 30's and 60's.

STORAGE INSTRUCTIONS:
Store below 25°C in blister strips. Protect from light and moisture.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
To be allocated.

NAME AND BUSINESS ADDRESS OF APPLICANT:
CIPLA MEDPRO (PTY) LTD
Rosen Heights,
Pasita Street,
Rosen Park,
Bellville,
7530

DATE OF PUBLICATION OF THIS PACKAGE INSERT: