PI for NEZOLAP TABLETS

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

NEZOLAP 2,5 mg (film-coated tablet)

NEZOLAP 5 mg (film-coated tablet)

NEZOLAP 10 mg (film-coated tablet)

NEZOLAP ODT 5 mg (orally disintegrating tablet)

NEZOLAP ODT 10 mg (orally disintegrating tablet)

NEZOLAP ODT 15 mg (orally disintegrating tablet)

NEZOLAP ODT 20 mg (orally disintegrating tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NEZOLAP 2,5 mg

Each film-coated tablet contains 2,5 mg olanzapine

Sugar free.

NEZOLAP 5 mg

Each film-coated tablet contains 5 mg olanzapine

Sugar free.

NEZOLAP 10 mg

Each film-coated tablet contains 10 mg olanzapine

Sugar free.

NEZOLAP ODT 5 mg

Each orally disintegrating tablet contains 5 mg olanzapine

Contains aspartame (0,125 mg).

NEZOLAP ODT 10 mg

Each orally disintegrating tablet contains 10 mg olanzapine

Contains aspartame (0,25 mg)

NEZOLAP ODT 15 mg

Each orally disintegrating tablet contains 15 mg olanzapine

Contains aspartame (0,375 mg)

NEZOLAP ODT 20 mg

Each orally disintegrating tablet contains 20 mg olanzapine

Contains aspartame (0,375 mg

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

NEZOLAP 2,5 mg

White to off white coloured, round shaped, biconvex, film-coated tablets having 'CL' debossed on one side and '39' on other side.

NEZOLAP 5 mg

White to off white coloured, round shaped, biconvex, film-coated tablets having ‘CL 40’ debossed on one side and plain on other side.

NEZOLAP 10 mg

White to off white coloured, round shaped, biconvex, film-coated tablets having ‘CL 42’ debossed on one side and plain on other side.

Orally disintegrating tablet.

This is rapid-dispersing preparation to be placed in the mouth or alternatively to be dispersed in water or other suitable beverage for administration.

NEZOLAP ODT 5 mg

Yellow, round shaped, biconvex, uncoated tablets having ‘ML 35’ debossed on one side and plain on other side.

NEZOLAP ODT 10 mg

Yellow, round shaped, biconvex, uncoated tablets having ‘ML 36’ debossed on one side and plain on other side.

NEZOLAP ODT 15 mg

Yellow, round shaped, biconvex, uncoated tablets having ‘ML 37’ debossed on one side and plain on other side.

NEZOLAP ODT 20 mg

Yellow, round shaped, biconvex, uncoated tablets having ‘CL 1’ debossed on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEZOLAP is indicated for the treatment of manifestations of psychotic disorders.

The antipsychotic efficacy of olanzapine was established in controlled trials of schizophrenic inpatients 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).

It is recommended that responding patients be continued on **NEZOLAP** at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

NEZOLAP is further indicated for the treatment of an acute episode of moderate to severe mania and for preventing recurrence of manic episodes of bipolar disorder.

4.2 Posology and method of administration

Posology:

Psychotic Disorders:

NEZOLAP tablets and **NEZOLAP ODT** 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.

In order to evaluate efficacy and guard against side effects, dosage increases should not be considered before one week, since steady state for olanzapine would not be achieved for approximately one week. The dose range is from 5 mg to 20 mg per day. Increasing the dose over the routine daily dose of 10 mg is advised only after appropriate clinical assessment.

Acute mania in bipolar disorder:

NEZOLAP and NEZOLAP ODT should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 mg.

Dosage adjustments within the dose range of 5 mg to 20 mg per day, if indicated, should generally occur at intervals of not less than 24 hours.

Preventing recurrence in bipolar disorder:

The recommended starting dose is 10 mg per day. For patients who have been receiving **NEZOLAP and NEZOLAP ODT** for treatment of manic episode, continue therapy for preventing recurrence at the same dose. An increase to a dose greater than the recommended starting dose, within the range of 5 mg - 20 mg per day, is advised only after appropriate clinical assessment and should generally occur at intervals of not less than 24 hours.

The safety of dosages above 20 mg per day has not been evaluated in clinical trials.

Gradual tapering of the dose should be considered when discontinuing **NEZOLAP and NEZOLAP ODT** (see Section 4.4).

Special Populations:

Elderly

A lower starting dose should be considered in the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to **NEZOLAP** (see section 4.4).

Hepatic Impariment

A 5 mg starting dose should be considered for patients with moderate hepatic impairment (see section 4.4).

Renal Impairment

Dosage adjustment based upon the degree of renal impairment is not required (see section 5.2).

Paediatric population

Safety and efficacy in patients under the age of 18 years have not been established.

Method of administration:

Oral, without regard to meals**.**

NEZOLAP ODT should be placed in the mouth, where they will rapidly disperse in the saliva, so they 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 suitable beverage (orange juice, apple juice, milk or coffee) immediately before administration.

4.3 Contraindications

NEZOLAP is contraindicated:

- in patients with known hypersensitivity to olanzapine or any of its ingredients. (see Section 6.1)
- in patients with a known risk for narrow-angle glaucoma.

Paediatric use: Safety and efficacy in patients younger than 18 years of age have not been established.

4.4 Special warnings and precautions for use

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 **NEZOLAP**.

Patients with an established diagnosis of diabetes mellitus who are started on **NEZOLAP** should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (obesity, familial history of diabetes) who are initiating treatment with **NEZOLAP** should be monitored

for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with **NEZOLAP** should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when **NEZOLAP** was discontinued, however, some patients required ongoing antidiabetic treatment despite discontinuation of therapy with **NEZOLAP**.

Discontinuation:

Discontinuation reactions may occur, usually within a week of discontinuing **NEZOLAP**. These reactions may consist of a cholinergic syndrome (diaphoresis, diarrhoea, sialorrhoea, nausea and vomiting, anxiety, agitation, insomnia and tremor). **NEZOLAP** should therefore be gradually discontinued.

Hyperprolactinaemia:

NEZOLAP causes an increase in prolactin levels and the elevation persists during chronic administration.

Neuroleptic malignant syndrome (NMS):

NMS has occurred infrequently in association with **NEZOLAP.**

NMS is a potentially fatal symptom complex. 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. **NEZOLAP** should be discontinued should any of the clinical manifestations of NMS or high fever without additional clinical manifestations of NMS be observed.

Seizures:

NEZOLAP should be used with caution in patients with a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur in some patients treated with **NEZOLAP**.

Tardive dyskinesia:

NEZOLAP has been associated with a low incidence of treatment emergent dyskinesia. If signs or symptoms of tardive dyskinesia appear in a patient on **NEZOLAP**, a dose reduction or discontinuation should be considered. However, some patients may benefit from continued treatment with **NEZOLAP** despite the presence of the syndrome. The risk of tardive dyskinesia increases with long-term exposure and symptoms can temporarily deteriorate or even arise after discontinuation of treatment.

Transaminase elevations and hepatic impairment:

Transient elevations of liver transaminases (ALT, AST) have been observed. Caution should be exercised in patients with elevated ALT and/or AST sign 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.

Periodic assessment of transaminases is recommended in patients with significant hepatic disease. A 5 mg starting dose should be considered for patients with moderate hepatic impairment.

In the event of elevated liver transaminases, ALT and/or AST during treatment, follow-up should be organised and dose reduction should be considered. In cases where hepatitis has been diagnosed, **NEZOLAP** treatment should be discontinued.

Safety experience in elderly patients with dementia-related psychosis:

The efficacy of **NEZOLAP** has not been established in elderly patients with dementia-related psychosis. 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. Abnormal gait and falls were very common (> 10 %), urinary incontinence and respiratory infection were very common and there was an increased incidence in cerebrovascular incidence including stroke. Risk factors that may predispose this patient population to increased mortality when treated with **NEZOLAP** include age ≥ 80 years, sedation, concomitant use of benzodiazepines or presence of pulmonary conditions (i.e. 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 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. **NEZOLAP** is not approved for the treatment of patients with dementia-related psychosis.

Lipid alterations:

Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials. Lipid alterations should be managed as clinically appropriate, particularly in dyslipidaemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with **NEZOLAP**, should be monitored regularly for lipids e.g., at baseline, 12 weeks after starting **NEZOLAP** treatment and every 5 years thereafter.

QT interval:

In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post-baseline in patients with baseline QTcF< 500 msec) were uncommon (0,1 % to 1 %) in patients treated with olanzapine as contained in **NEZOLAP**, with no significant differences in associated cardiac events compared to placebo. However, caution should be exercised when **NEZOLAP** 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, hypokalaemia or hypomagnesaemia.

Thromboembolism:

Temporal association of olanzapine treatment and venous thromboembolism (VTE) has been reported uncommonly (≥ 0,1 % and < 1 %). 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, **NEZOLAP** may antagonise the effects of direct and indirect dopamine agonists.

Sudden cardiac death:

In post-marketing reports with olanzapine as contained in **NEZOLAP**, the event of sudden cardiac death has been reported. In a retrospective observational cohort study, the risk of presumed sudden cardiac death in patients treated with olanzapine was approximately twice the risk in patients not using antipsychotics. In the study, the risk of olanzapine was comparable to the risk of atypical antipsychotics included in a pooled analysis.

Concomitant illnesses:

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

Olanzapine 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. There is an increased prevalence of diabetes amongst patients with schizophrenia. Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during olanzapine treatment. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for developing diabetes mellitus.

NEZOLAP is not recommended in Parkinson's disease due to a possible increase in parkinsonian symptoms and hallucinations.

Orthostatic hypotension:

NEZOLAP may induce orthostatic hypotension associated with dizziness, tachycardia and in some patients, syncope, especially during the initial treatment period.

Because of the risk of orthostatic hypotension with **NEZOLAP**, caution should be observed in cardiac patients.

Renal impairment:

See “Section 5.2”.

Body temperature regulation:

Disruption of the body's ability to reduce core body temperature has been associated with **NEZOLAP**. Appropriate care is advised when prescribing **NEZOLAP** for patients who will be experiencing conditions which may contribute to an elevation in core body temperature.

Dysphagia:

Oesophageal dysmotility and aspiration have been associated with antipsychotic medicines. **NEZOLAP** should be used with caution in patients at risk for aspiration pneumonia.

Suicide: The possibility of suicide attempt is inherent in schizophrenia and close supervision of high risk patients should accompany **NEZOLAP** treatment.

Haematology:

Caution should be exercised when administering **NEZOLAP** to patients with the following conditions:

- In patients with low leucocyte or neutrophil counts due to any reason.
- In patients with history of medicine induced bone marrow depression/toxicity.
- In patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy.
- In patients with hypereosinophillic condition or with myeloproliferative disease.

Elderly:

Clinical studies, in general, did not indicate that olanzapine was tolerated differently in the elderly compared to younger adults. However, a lower starting dose should be considered in the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to

NEZOLAP. As postural hypotension was infrequently observed in the elderly in clinical trials, it is recommended that blood pressure is measured periodically in patients over 65 years.

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.

Phenylalanine

NEZOLAP ODT contains aspartame, which is a source of phenylalanine. It may be harmful to people with phenylketonuria.

4.5 Interaction with other medicines and other forms of interaction

Caution should be exercised when **NEZOLAP** is taken in combination with other centrally acting medicines (especially those that can cause CNS depression) and alcohol. As it exhibits *in vitro* dopamine antagonism, **NEZOLAP** may antagonise the effects of levodopa and dopamine agonists. Because of the potential for inducing hypotension, **NEZOLAP** may enhance the effects of certain antihypertensive medicines.

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

Potential for other medicines to affect NEZOLAP:

The concomitant administration of activated charcoal reduces the oral bioavailability of olanzapine by 50 - 60 %.

Oral olanzapine administration was not associated with a persistent increase in absolute QTc intervals in clinical trials. Caution should be exercised when **NEZOLAP** is administered with medicines known to increase the QTc intervals, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) in combination with **NEZOLAP** (5 mg single dose) causes an increase (mean 16 %) in the maximum concentration of olanzapine and a

decrease (mean 16 %) in olanzapine clearance. The effect of repeat dosages or higher dosages of **NEZOLAP** has not been evaluated. Combination therapy is not advised.

Induction of CYP1A2:

The metabolism of olanzapine may be induced by concomitant smoking or carbamazepine therapy causing subsequent slightly to moderately lower olanzapine plasma levels. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of **NEZOLAP** may be considered if necessary.

Inhibition of CYP1A2:

Known potent inhibitors of CYP1A2 activity may reduce olanzapine clearance. Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. A lower starting dose of **NEZOLAP** 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 **NEZOLAP** should be considered if treatment with an inhibitor of CYP1A2 is initiated.

4.6 Fertility, pregnancy and lactation

Safety of **NEZOLAP** in pregnancy and lactation has not been established.

Pregnancy:

There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their medical practitioner if they become pregnant or intend to become pregnant during treatment with **NEZOLAP**.

New born infants exposed to **NEZOLAP** during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breastfeeding:

In a study in breastfeeding, 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 breastfeed an infant if they are taking **NEZOLAP**.

Fertility

Effects on fertility are unknown.

4.7 Effects on ability to drive and use machines

NEZOLAP may cause somnolence and dizziness; patients should be cautioned about operating machinery, including motor vehicles until they are reasonably certain that **NEZOLAP** therapy does not affect them adversely.

4.8 Undesirable effects

The following adverse reactions have been reported in association with **NEZOLAP**:

System Organ Class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Frequent	Eosinophilia, neutropenia, Leucopoenia
	Less Frequent	Thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity
Metabolism and nutrition disorders	Frequent	Peripheral oedema Weight gain, elevated cholesterol levels, elevated glucose levels, elevated triglyceride levels, glucosuria, increased appetite
	Less frequent	Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases,

System Organ Class	Frequency	Undesirable effects
		hypothermia
Nervous system disorders	Frequent	Dizziness, akathisia, somnolence, Parkinsonism, abnormal gait, falls, hallucinations, speech disorder, tremor
	Less frequent	Seizures, dystonia (including oculogyration), tardive dyskinesia amnesia, dysarthria, stuttering, Restless Legs Syndrome, neuroleptic malignant syndrome, discontinuation symptoms
Cardiac disorders	Frequent	Tachycardia
	Less frequent	Bradycardia, venous thromboembolism, QTc prolongation, ventricular tachycardia / fibrillation, sudden death
Vascular disorders	Frequent	Orthostatic hypotension
	Less frequent	Thromboembolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal disorders	Less frequent	Epistaxis, pneumonia
Gastrointestinal disorders	Frequent	Dry mouth, constipation
	Less frequent	Pancreatitis, abdominal distension

System Organ Class	Frequency	Undesirable effects
Hepatobiliary disorders	Frequent	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment
	Less frequent	Hepatitis (including hepatocellular, cholestatic or mixed liver injury)
Skin and subcutaneous tissue disorders	Less frequent	Rash Photosensitivity reaction, alopecia, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia
	Less frequent	Rhabdomyolysis
Renal and urinary disorders	Less frequent	Urinary incontinence, urinary retention, urinary hesitation
Pregnancy, puerperium and perinatal conditions	Frequency unknown	Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	Frequent	Erectile dysfunction in males, decreased libido in males and females
	Less frequent	Priapism Amenorrhea, in females, gynaecomastia /breast enlargement in males, neonatal drug withdrawal syndrome, breast enlargement galactorrhoea

System Organ Class	Frequency	Undesirable effects
General disorders and administration site conditions	Frequent	Asthenia, fatigue, oedema, pyrexia
Investigations	Frequent	ALT/SGPT - increased, AST/SGOT - increased, prolactin increased, increased alkaline phosphatase, high creatine phosphokinase, high Gamma Glutamyltransferase, high uric acid
	Less frequent	Increased total bilirubin

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Signs and symptoms: Very common symptoms reported in **NEZOLAP** 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 **NEZOLAP** overdose include delirium, convulsion, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2 % of overdose cases) and cardiopulmonary arrest.

Treatment:

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. 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.

Induction of emesis is not recommended.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible dysrhythmias.

There is no specific antidote to **NEZOLAP.** 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 medicines. Do not use adrenaline (epinephrine), dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced α-blockade. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

Pharmaceutical groups: A 2.6.5 Tranquillisers - miscellaneous structures.

ATC code: N05AH03

5.1 Pharmacodynamic properties

Olanzapine is an atypical antipsychotic, antimanic and mood-stabilising medicine having affinity for $5HT_{2A/2C}$, $5HT_3$, $5HT_6$, dopamine D_4, D_3, D_1, D_2, cholinergic muscarinic receptors (m_1 - m_5), α_1-adrenergic and histamine H_1 receptors.

Further studies also demonstrate that olanzapine selectively interacts with the mesolimbic system without significantly interacting with the extrapyramidal system. In experimental animals, 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 response 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 - m_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 $\alpha_1$receptors may explain the orthostatic hypotension observed with this medicine.

5.2 Pharmacokinetic properties

Absorption

Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food.

Distribution

The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1 000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Biotransformation

Olanzapine is metabolised 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. Other metabolites include the N-desmethyl and 2-hydroxymethyl metabolites, neither of which have *in vivo* pharmacological activity. The predominant pharmacologic activity is from the parent compound.

Elimination

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

Special populations

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 non-elderly subjects (< 65 years). Caution should be exercised in dosing the elderly, especially if there are other 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 population. 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.

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 haemodialysis. The effect of renal impairment on metabolite elimination has not been studied.

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 mg/kg (mice) and 175 mg/kg (rats). Dogs tolerated single oral doses up to 100 mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured 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 anaemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [area under the curve] 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. Oestrous 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 foetal 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 List of excipients

NEZOLAP tablets contains crospovidone, low substituted hydroxypropyl cellulose (L-HPC-LH-11), magnesium stearate, microcrystalline cellulose. The tablets are coated with coating made up of lecithin (soya), polyvinyl alcohol partly hydrolysed, talc, titanium dioxide (CI 77891), xanthan gum.

NEZOLAP ODT contains aspartame, crospovidone, low substituted hydroxypropyl cellulose (L-HPC-LH-11), magnesium stearate and microcrystalline cellulose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

NEZOLAP tablets: 36 months from the manufacturing date.

NEZOLAP ODT: 36 months from the manufacturing date.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep the blisters in the carton until required for use.

Keep the HDPE container tightly closed.

Store in the original package in order to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

1) <u>Blister Pack:</u>

Tablets are packed in cold form laminate 25 µ OPA/ 45 µ aluminium foil / 60 µ PVC as the forming material and 25 µ Aluminium plain foil/ 6-8 gsm heat seal lacquered as the lidding material, packed in a pre-printed carton.

Pack size include 10, 28 or 30 tablets.

2) <u>HDPE Container Pack:</u>

NEZOLAP Tablets are packed in 60 ml white round HDPE container with 33 mm neck finish which are closed with 33 mm child resistant closure with pulp and heat seal liner and packed in outer carton. Each HDPE container contains 1 sachet of 1 g silica gel.

NEZOLAP ODT are packed in 40 ml or 60 ml white round HDPE container with 33 - 400 mm neck finish which are closed with 33 mm child resistant closure with pulp and heat seal liner and packed in outer carton. Each HDPE container contains 1 sachet of 1 g silica gel.

Pack size include 28 or 30 tablets.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

NEZOLAP 2,5 mg: 47/2.6.5/0284
NEZOLAP 5 mg: 47/2.6.5/0285
NEZOLAP 10 mg: 47/2.6.5/0286
NEZOLAP ODT 5 mg: 48/2.6.5/0343
NEZOLAP ODT 10 mg: 48/2.6.5/0344
NEZOLAP ODT 15 mg: 48/2.6.5/0345
NEZOLAP ODT 20 mg: 48/2.6.5/0346

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 March 2021

10. DATE OF REVISION OF THE TEXT

05 APRIL 2023

PM0052-01

Vanita Rajool

Digitally signed by Vanita Rajool
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Date: 2023.06.29 08:19:21 +02'00'