PRODUCT NAME : Phrenpe	COUNTRY : South Africa	LOCATION : Indrad	Supersedes A/W No.:		
ITEM / PACK : PIL	NO. OF COLORS: 1	REMARK :			
DESIGN STYLE : Front / Back	PANTONE SHADE NOS.:	SUBSTRATE :			
CODE : xxxxxxxxx-6513	Black	Activities	Department	Name	Signature	Date
DIMENSIONS (MM) : 300 x 670 mm		Prepared By	Pkg.Dev			
ART WORK SIZE : S/S		Reviewed By	Pkg.Dev			
DATE : 17-07-2021		Approved By	Quality			

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.

Claudia Law - Approved - 19.07.2021

Tsiane Makou - Approved - 27.07.2021

Professional Information xxxxxxxx-6513

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE
PHRENPE 5 (5 mg) and PHRENPE 10 (10 mg) orodispersible tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
PHRENPE 5 mg orodispersible tablets:
Each orodispersible tablet contains 5 mg olanzapine. Contains sweetener: 1,20 mg aspartame.
Contains sugar: 41,80 mg mannitol (a sugar alcohol)
PHRENPE 10 mg orodispersible tablets:
Each orodispersible tablet contains 10 mg olanzapine. Contains sweetener: 2,40 mg aspartame. Contains sugar: 83,60 mg mannitol (a sugar alcohol)
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Orodispersible tablets.
PHRENPE 5 mg orodispersible tablets:
Yellow coloured, round, flat, bevel edged uncoated tablets with score line on side and debossed "5" on other side.
PHRENPE 10 mg orodispersible tablets:
Yellow coloured, round, flat, bevel edged uncoated tablets with score line on side and debossed "10" on other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
PHRENPE orodispersible tablets are indicated for the management of the 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 affect, emotional and social withdrawal, poverty of speech). It is recommended that responding patients be continued on PHRENPE at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment. PHRENPE is also indicated for the treatment of an acute episode of moderate to severe mania and for preventing recurrence of manic or depressive episodes of bipolar disorder.

4.2 Posology and method of administration
Posology
Psychotic disorders
PHRENPE orodispersible tablets should be administered on a once-a-day schedule without regards 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 disorders
PHRENPE should be administered on a once-a-day schedule without regards 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 PHRENPE 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 to 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 doses above 20 mg/day has not been established. Gradual tapering of the dose should be considered when discontinuing PHRENPE (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 PHRENPE (see section 4.4).
Hepatic impairment: A lower starting dose (5 mg) should be considered for these 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 (see section 4.4).
Renal impairment: Dosage adjustment based upon the degree of renal impairment is not required (see section 5.2).
Paediatric population: PHRENPE is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

Method of administration
PHRENPE orodispersible tablets 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
- Hypersensitivity to olanzapine (the active substance) or to any of the excipients listed in section 6.1.
- Patients with known risk or narrow-angle glaucoma.
- Children and adolescents below 18 years of age as safety and efficacy have not been established.

4.4 Special warnings and precautions for use
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.
Discontinuation of treatment
Discontinuation reactions may occur, usually within a week of discontinuing PHRENPE. These reactions may consist of a cholinergic syndrome (diaphoresis, diarrhoea, sialorrhoea, nausea and vomiting, anxiety, agitation, insomnia and tremor). PHRENPE treatment should therefore be discontinued gradually.
Hyperprolactinaemia
Olanzapine elevates prolactin levels and a modest elevation persist during chronic administration. An increase in the occurrence of breast cancers may be a result of these increases prolactin levels.
Elderly use
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 olanzapine, as contained in PHRENPE. 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.
Safety experience in elderly patients with dementia-related psychosis
In elderly patients with dementia-related psychosis, the efficacy of olanzapine, as contained in PHRENPE, has not been established. In olanzapine 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). Abnormal gait and falls were very common (> 10 %), urinary incontinence and respiratory infection were common, and there was an increased incidence in cerebrovascular incidents, including stroke. Risk factors that may predispose this patient population to increased mortality when treated with olanzapine as contained in PHRENPE, 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. PHRENPE is not approved for the treatment of patients with dementia-related psychosis.
Parkinson's disease
Olanzapine is not recommended in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease, as its use has been associated with an increase in parkinsonian symptoms and hallucinations and in clinical trials was no more effective than placebo in the treatment of psychotic symptoms.
Neuroleptic Malignant Syndrome (NMS)
Neuroleptic Malignant Syndrome (NMS) is a potentially life-threatening condition associated with the use of antipsychotic medicinal products, such as olanzapine. The symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability seen as irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia. Elevated serum creatine phosphokinase levels, myoglobinuria (rhabdomyolysis), and acute renal failure may also occur. PHRENPE should be discontinued if any of the clinical manifestations of NMS, or high fever without additional clinical manifestations of NMS, are observed.
Hyperglycaemia and diabetes
Hyperglycaemia and/or the development or worsening of diabetes, occasionally associated with ketoacidosis or coma, or death, has been uncommonly reported in patients treated with olanzapine. A prior increase in body weight has been reported in some cases, which may be a predisposing factor. Measuring of blood glucose levels at the start of PHRENPE treatment, 12 weeks after starting treatment, and annually thereafter is advisable. Patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are started on PHRENPE should be monitored regularly for worsening of glucose control. Patients who are started on PHRENPE should be observed for signs and symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia, and weakness. The weight of the patient should be monitored frequently, e.g. at the start of PHRENPE treatment, 4,8 and 12 weeks after the start of treatment and quarterly thereafter.
Lipid alterations
Patients who are treated with PHRENPE, may observe undesirable alterations of lipid levels. Patients who are treated with PHRENPE, should be monitored regularly for lipid levels, e.g. at the start of PHRENPE treatment, 12 weeks after the start of treatment and every 5 years thereafter.
Anticholinergic activity
Since olanzapine has shown anticholinergic activity *in vitro*, caution is advised when prescribing PHRENPE to patients with prostatic hypertrophy or paralytic ileus and related conditions.
Transaminase elevations and hepatic function
Transient and asymptomatic elevations of hepatic aminotransferases namely ALT and/or AST have been seen commonly, especially in early treatment with olanzapine. Caution should be exercised in patients with elevated levels of ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients who are being treated with potentially hepatotoxic medicines and in patients with pre-existing conditions associated with limited hepatic functional reserve. In these instances, a follow-up should be organised to conduct further tests. A 5 mg starting dose should be considered for patients with moderate hepatic impairment (see section 4.2). Treatment with PHRENPE should be discontinued in cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed. In the event of raised alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels during treatment, a dose reduction should be considered.
Neutropenia
Caution should be exercised in patients with low leucocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy and chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used simultaneously (see section 4.8).
QT interval
Caution should be exercised when prescribing PHRENPE with medicines that are known to increase QTc interval (see section 4.5: Interaction with other medicinal products and other forms of interaction), especially in the elderly, in patients with congenital long QT syndrome, heart hypertrophy, congestive heart failure, hypomagnesaemia or hypokalaemia.
Thromboembolism
Patients with schizophrenia often present with acquired risk factors for venous thromboembolism. Thus, all possible risk factors of venous thromboembolism should be identified (e.g. immobilisation of patients), and preventative measures be undertaken.
General CNS activity
Given the primary central nervous system (CNS) effects of olanzapine, caution should be used when using PHRENPE in combination with other centrally acting medicines and alcohol. PHRENPE may antagonise the effects of direct and indirect dopamine agonists, as olanzapine has shown to exhibit *in vitro* dopamine antagonism (see section 4.5).
Seizures
Seizures have been reported to occur uncommonly in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported. PHRENPE should thus be used with caution in patients with a history of seizures or a decreased seizure threshold.
Tardive dyskinesia
There is a low incidence of treatment emergent dyskinesia in patients treated with olanzapine. The risk of tardive dyskinesia however increases with long-term exposure. A dose reduction or discontinuation of treatment with PHRENPE should be considered if signs or symptoms of tardive dyskinesia appear. Symptoms can deteriorate temporarily or even arise after discontinuation of treatment.
Orthostatic hypotension
PHRENPE may induce orthostatic hypotension which is associated with dizziness, tachycardia in some patients and syncope. This can occur especially during the initial treatment period. Because PHRENPE carries the risk of causing orthostatic hypotension, caution should be observed in cardiac patients.
Body temperature regulation
Antipsychotic medications may disrupt the body's ability to lower core body temperature, thus increasing the risk of heatstroke. Appropriate care is advised in conditions which may contribute to an elevation in core body temperature, such as exposure to extreme heat and strenuous exercise.
Dysphagia
There is in increased risk of aspiration and oesophageal dysmotility when using antipsychotic medicines. PHRENPE should be used with caution in patients at risk of aspiration pneumonia.
Suicide
Careful supervision of patients with suicidal tendencies is recommended in high-risk patients, since the possibility of a suicide attempt is inherent in schizophrenia.
Sudden cardiac death
Sudden cardiac death has been reported in patients using olanzapine as was seen during post marketing reports.

Paediatric population
PHRENPE is not recommended for use in children and adolescents below 18 years of age.
Phenylalanine
PHRENPE tablets contain aspartame, which is a source of phenylalanine. Phenylalanine may be harmful for people with phenylketonuria.
Mannitol
PHRENPE orodispersible tablets contain mannitol. This may cause a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction
Potential interactions affecting olanzapine
Olanzapine is metabolised by the isoenzyme CYP1A2. Substances that can specifically induce or inhibit CYP1A2 may therefore affect the pharmacokinetic of olanzapine.
Induction of CYP1A2
Simultaneous use with carbamazepine and/or the smoking of cigarettes may induce the metabolism of olanzapine, which may lead to reduced concentrations of olanzapine. Clinical monitoring of the patient is recommended, and an increase of PHRENPE dose may be considered if necessary.
Inhibition of CYP1A2
Fluvoxamine, which is a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine, which leads to higher concentrations of olanzapine. A lower starting dose of PHRENPE should be considered in patients who are also using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of PHRENPE should be considered if treatment with an inhibitor of CYP1A2 is initiated.
Decreased bioavailability
The bioavailability of olanzapine is reduced by 50 – 60 % when taken concomitantly with activated charcoal. Activated charcoal should be taken at least 2 hours before or after PHRENPE. 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 (see section 4.4). Olanzapine does not inhibit the main CYP450 isoenzymes *in vitro*. No inhibition of metabolism was found for the following substances, as verified through *in vivo* studies: tricyclic antidepressants (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19). Olanzapine showed no interaction when administered simultaneously with lithium or biperiden. No dosage adjustment is necessary for valproate when concomitantly administered with olanzapine. Because of the potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents. Given the extensive clinical and *in vitro* studies, olanzapine would not be expected to interfere with the metabolism of most medicines.
General CNS activity
Given the primary central nervous system (CNS) effects of olanzapine, caution should be used when using PHRENPE in combination with other centrally acting medicines and alcohol (see section 4.4). It is not recommended to use olanzapine together with anti-Parkinsonian medicine in patients with Parkinson's disease and dementia (see section 4.4).
QTc interval
Caution should be exercised when prescribing PHRENPE with medicines that are known to increase QTc interval (see section 4.4).

4.6 Fertility, pregnancy and lactation
Women of childbearing potential
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with PHRENPE.
Pregnancy
There are no adequate and well-controlled studies in pregnant women. Newborn infants exposed to antipsychotics (including olanzapine) 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. Newborns should thus be monitored closely.
Breastfeeding
Olanzapine is excreted in human breastmilk. Patients should be advised not to breastfeed their babies if they are taking PHRENPE.
Fertility
The effects on fertility are unknown.

4.7 Effects on ability to drive and use machines
PHRENPE may cause somnolence and dizziness. Patients should be cautioned about operating machinery, including motor vehicles until they are certain that treatment with PHRENPE will not affect them.

4.8 Undesirable effects
a. Summary of the safety profile: The most frequently reported adverse reactions associated with the use of olanzapine are somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels, glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia, dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases, rash, asthenia, fatigue, pyrexia, arthralgia, increased alkaline phosphatase, high gamma glutamyltransferase, high uric acid, high creatine phosphokinase and oedema.
b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Frequent	Eosinophilia. Leukopenia. Neutropenia.
	Less frequent	Thrombocytopenia.
Immune system disorders	Less frequent	Hypersensitivity.
Metabolism and nutrition disorders	Frequent	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. Hypothermia.
Nervous system disorders	Frequent	Somnolence. Dizziness. Akathisia. Parkinsonism. Dyskinesia.
	Less frequent	Seizures where in most cases a history of seizures or risk factors for seizures were reported.Dystonia (including oculogyration).Tardive dyskinesia.Amnesia. Dysarthria. Stuttering. Restless Legs Syndrome. Neuroleptic malignant syndrome. Discontinuation symptoms.
Cardiac disorders	Less frequent	Bradycardia. 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.
Gastrointestinal disorders	Frequent	Mild, transient anticholinergic effects including constipation and dry mouth.
	Less frequent	Abdominal distension. Pancreatitis.
Hepato-biliary 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	Frequent	Rash.
	Less frequent	Photosensitivity reaction. Alopecia.
	Frequency unknown	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	Amenorrhea. Breast enlargement. Galactorrhea in females. Gynaecomastia/breast enlargement in males. Priapism.
General disorders and administration site conditions	Frequent	Asthenia. Fatigue. Oedema. Pyrexia.
Investigations	Frequent	Elevated plasma prolactin levels. Increased alkaline phosphatase. High creatine phosphokinase. High gamma glutamyltransferase. High uric acid.
	Less frequent	Increased total bilirubin.

c. Description of selected adverse reactions
Gradual tapering of the dose should be considered when discontinuing PHRENPE (see section 4.4). Abrupt discontinuation of PHRENPE treatment may lead to acute symptoms such as sweating, diarrhoea, excessive salivation, anxiety, agitation, nausea, vomiting, insomnia and tremors. PHRENPE treatment should therefore be discontinued gradually.
d. Other special population(s)
The table below summarises adverse reactions observed when olanzapine was given to elderly patients with dementia of the Alzheimer's type:

MedDRA system organ class	Frequency	Adverse reactions
Psychiatric disorders	Frequent	Visual hallucinations.
Nervous system disorders	Frequent	Abnormal gait. Falls.
Respiratory, thoracic and mediastinal disorders	Frequent	Pneumonia.
Skin and subcutaneous tissue disorders	Frequent	Erythema.
Renal and urinary disorders	Frequent	Urinary incontinence.
General disorders and administration site conditions	Frequent	Lethargy.
Investigations	Frequent	Increased body temperature.

The table below summarises adverse reactions observed in patients with medicines-induced (dopamine agonist) psychosis associated with Parkinson's disease:

MedDRA system organ class	Frequency	Adverse reactions
Psychiatric disorders	Frequent	Hallucinations.
Nervous system disorders	Frequent	Parkinsonian symptomatology.

The table below summarises adverse reactions observed when olanzapine was given to patients with bipolar mania that was also receiving lithium or valproate:

MedDRA system organ class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Frequent	Weight gain. Increased appetite.
Nervous system disorders	Frequent	Speech disorder. Tremor.
Gastrointestinal disorders	Frequent	Dry mouth.

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 with olanzapine 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 olanzapine overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrythmias (< 2 % of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg, but survival has also been reported following acute overdose of approximately 1 500 mg of oral olanzapine.
Management
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. 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 PHRENPE; 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. Induction of emesis is not recommended. Do not use epinephrine, dopamine or other sympathomimetics with β-agonist activity, since β-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
5.1 Pharmacodynamic properties
A 2.6.5 Tranquillisers - miscellaneous structures. Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code N05A H03. Olanzapine is an atypical antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across several receptor systems. Olanzapine has shown to have affinity for serotonin ($5HT_{2A/2C}$, $5HT_3$ and $5HT_6$), dopamine (D_1, D_2, D_3, D_4 and D_5), cholinergic muscarinic (M_1-M_5), α_1 adrenergic and histamine H_1 receptors. Additional studies (electrophysiological studies) have also demonstrated that olanzapine selectively interacts with the mesolimbic system without significantly interacting with the extrapyramidal system. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side effects. Olanzapine increases response in an 'anxiolytic test'. In a single oral dose of 10 mg Positron Emission Tomography (PET) study in healthy volunteers, olanzapine demonstrated to have a higher occupancy for the serotonin $5HT_{2A}$ receptor than the dopamine D_2 receptor. Olanzapine's antagonism of the muscarinic receptors (M_1-M_5) may explain its anticholinergic effects, the antagonism of the histamine H_1 receptors may explain the somnolence that is experienced and its antagonism of the adrenergic α_1 receptors may explain the orthostatic hypotension observed with this medicine.

5.2 Pharmacokinetic properties
Absorption
Olanzapine is well absorbed after oral administration and is not affected by food. It reaches peak plasma concentrations within 5 to 8 hours.
Distribution
Olanzapine is predominantly bound to albumin and α_1-acid-glycoprotein. The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml.
Biotransformation
Metabolism of olanzapine occurs in the liver via conjugative and oxidative pathways. The major circulating metabolite is 10-N-glucoronide and 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 these metabolites exhibit significantly less *in vivo* pharmacological activity. The predominant pharmacologic activity is from the Olanzapine, the parent compound.
Elimination
Based on the results of studies done after oral administration, the elimination half-life of olanzapine in healthy subjects varied based on age and gender:

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

Based on the results of studies done in healthy elderly subjects (65 years and older) versus non-elderly subjects, the mean elimination half-life was prolonged, and the clearance reduced:

	Elderly (≥ 65 years)	Non-elderly
Elimination half-life	51,8 hours	33,8 hours
Clearance	17,5 l/hour	18,2 l/hour

Caution should be exercised in dosing the elderly, especially if there are other factors that might additively influence medicine metabolism and/or pharmacodynamic sensitivity. Based on the results of studies done in female versus male subjects, the mean elimination half-life was somewhat prolonged, and clearance reduced:

	Females	Males
Elimination half-life	36,7 hours	32,3 hours
Clearance	18,9 l/hour	27,3 l/hour

Olanzapine in the dose range of 5 – 20 mg, demonstrates a comparable safety profile when women are compared to men.

Special Population
Renal impairment
There is no significant difference in mean elimination half-life or clearance in renally impaired patients (creatinine clearance <10 ml/min) versus healthy patients:

	Renally impaired (< 10 ml/min)	Healthy
Elimination half-life	37,7 hours	32,4 hours
Clearance	21,2 l/hour	25,0 l/hour

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.

Hepatic impairment
Based on the results of studies done subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-life compared to subjects with no hepatic dysfunction.
Smoking
In non-smoking versus smoking subjects (males and females), the mean elimination half-life was prolonged, and the clearance was reduced:

	Non-smokers	Smokers
Elimination half-life	38,6 hours	30,4 hours
Clearance	18,6 l/hour	27,7 l/hour

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.

Haematologic toxicity
Based on the results of studies in mice and rats, it was concluded that no evidence of bone marrow cytotoxicity was found.
Reproductive toxicity
Based on the results of studies in rats, it was concluded that Olanzapine had no teratogenic effects.
Mutagenicity
In the studies done Olanzapine was found not to be 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:
Mannitol
Aspartame
Crospovidone (Polyplasdone XL-10)
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store at or below 25 °C. Store in the original package. Protect from light and moisture.

6.5 Nature and contents of container
PHRENPE 5 orodispersible tablets are available in Alu/Alu blisters (plain aluminium foil along with the cold form OPA/Alu/PVC foil) and peelable Alu/Alu blisters (blister of cold form blister [CFB] foil and paper backed peelable aluminium foil) in cartons of 10, 14, 28, 30, 35, 50, 56 or 70 tablets per carton. Not all pack sizes may be marketed. PHRENPE 10 orodispersible tablets are available in Alu/Alu blisters (plain aluminium foil along with the cold form OPA/Alu/PVC foil) and peelable Alu/Alu blisters (blister of cold form blister [CFB] foil and paper backed peelable aluminium foil) in cartons of 10, 14, 28, 30, 35, 50, 56 or 70 tablets per carton. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION
Trinity Pharma (Pty) Ltd.
106, 16th Road, Building 2, Midrand, Johannesburg, 1686, South Africa

8 REGISTRATION NUMBER(S)
PHRENPE 5: 47/2.6.5/0182
PHRENPE 10: 47/2.6.5/0183

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 06 April 2021

10 DATE OF REVISION OF THE TEXT
NA

Patient Information Leaflet

SCHEDULING STATUS

S5

PHRENPE 5 mg orodispersible tablets
PHRENPE 10 mg orodispersible tablets
Olanzapine

PHRENPE 5 contains sweetener: 1,20 mg aspartame
PHRENPE 5 contains sugar: 41,80 mg mannitol
PHRENPE 10 contains sweetener: 2,40 mg aspartame
PHRENPE 10 contains sugar: 83,60 mg mannitol

Read all of this leaflet carefully before you start taking PHRENPE
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- PHRENPE has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet
1. What PHRENPE is and what it is used for
2. What you need to know before you take PHRENPE
3. How to take PHRENPE
4. Possible side effects
5. How to store PHRENPE
6. Contents of the pack and other information

1. What PHRENPE is and what it is used for
PHRENPE contains the active substance olanzapine. PHRENPE acts as an antipsycotic, antimanic and mood stabiliser and is used to treat the following conditions:
- Displays of psychotic disorders such as schizophrenia.
- Acute episodes of moderate or severe manic episodes.
- Preventing reappearance of manic or depressive episodes of bipolar disorder.

2. What you need to know before you take PHRENPE
Do not take PHRENPE
- If you are hypersensitive (allergic) to olanzapine or any of the other ingredients of PHRENPE (listed in section 6).
- If you have a risk to develop or you have narrow-angle glaucoma (a condition where the pressure in your eye is increased).
- If you are younger than the age of 18 years.

Warnings and precautions
- Your doctor will monitor you closely during the initial stages of treatment to see if the medicine is working for you.
- Treatment with PHRENPE should be stopped gradually, by tapering your dose. If treatment is stopped suddenly, then you might experience symptoms such as sweating, diarrhoea, excessive drooling from the mouth, anxiety, agitation, nausea, vomiting, the inability to sleep and involuntary shaking.
- PHRENPE increases the levels of prolactin in your blood (prolactin is the hormone that tells the body to make breast milk when a person is pregnant or breastfeeding), and this may increase your chance of developing breast cancers.
- The levels of fat in your blood may be changed when using PHRENPE. Your doctor should monitor these levels regularly, for instance at the start of treatment, after 12 weeks and every 5 years after that.
- A condition known as tardive dyskinesia (involuntary, repetitive body movements which may include grimacing, stick out the tongue or smacking the lips) might occur when using PHRENPE for a long period of time. When this happens, your doctor should either lower your dose of PHRENPE or discontinue it. These symptoms can disappear temporarily or even appear even after the discontinuation of treatment.
- The use of PHRENPE may cause a condition known as orthostatic hypotension (fall in blood pressure when you stand up too quickly from a sitting or lying position and is associated with dizziness, increased heartbeat and in some patients a temporary loss of consciousness), especially during the start of treatment. Caution should be observed in patients with heart problems and your blood pressure should be measured regularly if you are 65 years and older.

Take special care with PHRENPE:
- if you are also using medicines to treat a condition known as Parkinson's disease. The symptoms you usually get from Parkinson's disease will be increased.
- if you develop any of the following symptoms:
  - a high fever,
  - muscle stiffness,
  - altered mental status,
  - irregular pulse or blood pressure,
  - increased heartbeat or irregular heartbeat or
  - unusually high sweating for no reason.

These symptoms might indicate that you have developed a life-threatening condition known as Neuroleptic Malignant Syndrome.
Speak to your doctor immediately if you think you are experiencing any of the above symptoms, even if you only have a high fever for no reason.
Your treatment with PHRENPE should be stopped immediately.
- if you have diabetes, as the use of PHRENPE might increase your sugar levels, that will worsen your diabetes.
  You might develop diabetes if you are overweight or have a family history of diabetes mellitus while you are using PHRENPE. Your doctor should monitor your blood sugar levels closely at the start of treatment, after 12 weeks and then once every year.
  You should speak to your doctor immediately if you develop any of the following symptoms when you start using PHRENPE as these might be symptoms related to diabetes:
  - excessive thirst,
  - passing abnormally large amounts of urine,
  - excessive eating or appetite or
  - weakness.
- if you have been told that you have dementia-related psychosis and/or behavioural disturbances and you:
  - are over 65 years of age,
  - have difficulty swallowing foods or liquids,
  - are using other medicines that causes sedation,
  - are malnourished or dehydrated,
  - have problems with your lungs, for instance pneumonia,
  - are also using a group of medicines known as benzodiazepines (used for to treat anxiety).
- if you have an enlarged prostate or an obstruction of the intestines due to paralysis of the intestinal muscles.
- if you have liver damage or are being treated with other medicines that might harm your liver.

Your doctor should do regular tests to determine if your liver is being affected while you take PHRENPE. Your treatment with PHRENPE should be stopped if you develop hepatitis (inflammation of the liver).
- if you have been told that you have low levels of white blood cells for any reason.
- if you are receiving any medicines that causes a condition that decreases white blood cell levels in your blood (also called neutropenia).
- if you have a history of drug-induced bone marrow depression or have bone marrow depression that is caused by a related illness.
- if you are receiving radiation therapy or chemotherapy (therapy used to treat cancer).
- if you have been told that you have high levels of a certain type of white blood cell in your blood (eosinophils) or have a disorder where your bone marrow makes too many abnormal red blood cells, white blood cells or platelets, which accumulate in your blood (myeloproliferative disease).
- if you are also using a medicine known as valproate (used to treat epilepsy), as this might lead to the neutropenia.
- if you are also using medicines that might increase your QT interval and you:
  - are 65 years or older,
  - have congenital long QT syndrome (a heart rhythm disorder that can potentially cause fast, chaotic heartbeats),
  - have an enlarged heart,
  - have congestive heart failure,
  - have low levels of magnesium or potassium in your blood.
- if you have possible risk factors that might lead to a venous thromboembolism such as being immobilized for long periods of time.
- when you are also using other centrally acting medicines and alcohol.
- if you have a history of seizures or have risk factors that might lead to seizures.
- if you are planning to do strenuous exercise or will be exposed to extreme heat, as your body's ability to lower its core body temperature may be disrupted. This may lead to heatstroke.
- as there is an increased risk of breathing in foods, liquids, saliva or vomit into the airways and decreased movement of the gullet.
- if you have suicidal tendencies. You should be monitored closely.
- if you have problems with your heart.

Children and adolescents
PHRENPE is not recommended for use in children and adolescents below the age of 18 years.

Other medicines and PHRENPE
Always tell your health care provider if you are taking any other medicine. (This includes all complementary or traditional medicines.)
In particular, tell your doctor if you are taking or have recently taken any of the following medicines and you are also taking PHRENPE:
- Carbamazepine – an increase of your PHRENPE dose might be necessary.
  You would possibly also need to increase your dose of PHRENPE if you smoke cigarettes.
- Fluvoxamine and/or ciprofloxacin – a lower starting dose of PHRENPE should be considered.
- Activated charcoal – the amount of PHRENPE concentrations in your blood is reduced by 50 – 60 % when taken with activated charcoal. Take activated charcoal at least 2 hours before you take PHRENPE.
- Medicines for Parkinson's disease – PHRENPE may reduce the effect of these medicines.
- Certain medicines used to treat high blood pressure – PHRENPE may enhance the effects of these medicines which may lead to patients experiencing very low blood pressure.
- Other centrally acting medicines and alcohol.

It is not recommended to use PHRENPE together with anti-Parkinsonian medicine in patients with Parkinson's disease and dementia.

Caution should be exercised when prescribing PHRENPE with medicines that are known to increase QT intervals.

PHRENPE with food, drink and alcohol
PHRENPE may be taken with or without food.
PHRENPE can be taken with water or any other suitable beverage such as orange juice, apple juice, milk or coffee. You may disperse your PHRENPE in these beverages just before you take it since they are orodispersible tablets.

PHRENPE should not be taken together with alcohol.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before taking this medicine. The following symptoms may occur in newborn babies, of mothers who have used PHRENPE during their third trimester of pregnancy: agitation, muscle stiffness and/or weakness, shaking, sleepiness, breathing problems and difficulty in feeding. If your baby develops any of these symptoms, you may need to contact your doctor. You should not be given PHRENPE while you are breastfeeding your baby as small amounts of olanzapine passes into breast milk. You should not breastfeed your baby while using PHRENPE.

Driving and using machines
PHRENPE may cause sleepiness and dizziness. It is thus advisable not to drive or use machines until you know how PHRENPE will affect you.
It is not always possible to predict to what extent PHRENPE may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which PHRENPE affects them.

PHRENPE contains aspartame
Patients who cannot take phenylalanine should not take PHRENPE as it contains aspartame which is a source of phenylalanine. It may be harmful for patients with phenylketonuria.

PHRENPE contains mannitol:
PHRENPE orodispersible tablets contain mannitol. This may cause a mild laxative effect.

3. How to take PHRENPE
Do not share medicines prescribed for you with any other person. Always take PHRENPE exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The safety of doses above 20 mg per day has not been established.

PHRENPE can be taken with or without food. PHRENPE orodispersible tablets are very fragile and should thus be taken immediately after removing it from the blister. PHRENPE orodispersible tablets should be placed in the mouth. It will dissolve directly in your mouth, so that it can be easily swallowed. You can also place the tablet in a full glass of water, orange juice, apple juice, coffee or milk. Drink it straight away.

For the use in psychotic disorders:
The usual starting dose is 5 mg to 10 mg per day (once-a-day schedule). The target dose should be 10 mg/day within several days. To guard against side effects and to evaluate if the medicine is working properly, the dose of PHRENPE should not be increased before one week has passed. 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.

For the use in acute mania in bipolar disorders:
The usual starting dose is 10 mg per day (once-a-day schedule). 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.

For the prevention of recurrence in bipolar disorder:
The recommended starting dose is 10 mg per day. If you have been receiving PHRENPE for the treatment of manic episodes, then continue your therapy by using the same dose to prevent it from reappearing again. An increase to a dose greater than the recommended starting dose, within the range of 5 mg to 20 mg per day, is advised only after appropriate clinical assessment and should generally occur at intervals of not less than 24 hours.

The use of PHRENPE is not recommended for use in children and adolescents below the age of 18 years.

Your doctor will tell you how long your treatment with PHRENPE will last. Treatment with PHRENPE should be stopped gradually, by tapering your dose. Do not stop treatment early because you might experience symptoms such as sweating, diarrhoea, excessive drooling from the mouth, anxiety, agitation, nausea, vomiting, the inability to sleep and involuntary shaking. If you have the impression that the effect of PHRENPE is too strong or too weak, tell your doctor or pharmacist.

If you take more PHRENPE than you should
In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.
Some of the symptoms that you might experience when you have taken more PHRENPE than you should include:
- increased heartbeat,
- feeling anxious or being aggressive,
- difficulty in speaking normally,
- various extrapyramidal symptoms which include shaking, slurred speech, uncontrollable or involuntary movement,
- reduced level of consciousness, which may range from being sedated to ending up in a coma,
- confused thinking and reduced awareness of the environment (delirium),
- fits (convulsions),
- possible neuroleptic malignant syndrome (symptoms include: a high fever, muscle stiffness, altered mental status, irregular pulse or blood pressure, increased heartbeat or irregular heartbeat, unusually high sweating for no reason),
- difficulty in breathing,
- increased risk of breathing in foods, liquids, saliva or vomit into the airways,
- increased or decreased blood pressure,
- irregular beating of the heart (too slow or too fast),
- heart attack.

If you forget to take PHRENPE
Do not take a double dose to make up for forgotten individual doses. Take your tablets as soon as you remember.

If you stop taking PHRENPE
Treatment with PHRENPE should be stopped gradually, by tapering your dose. If treatment is stopped suddenly, then you might experience symptoms such as sweating, diarrhoea, excessive drooling from the mouth, anxiety, agitation, nausea, vomiting, the inability to sleep and involuntary shaking.

4. Possible side effects
PHRENPE can have side effects.

Not all side effects reported for PHRENPE are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking PHRENPE, please consult your healthcare provider for advice.

If any of the following happens, stop taking PHRENPE and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips and mouth or throat, which may cause difficulty in swallowing or breathing,
- rash or itching,
- fainting.

These are all very serious side effects. If you have them, you may have had a serious reaction to PHRENPE. You may need urgent medical attention or hospitalisation.

Tell your doctor if you notice any of the following:
Adults:
Frequent side effects:
- sleepiness,
- weight gain,
- an increase of a certain type of white blood cell (eosinophils) in your body, known as eosinophilia,
- elevated levels of prolactin (prolactin is the hormone that tells the body to make breast milk when a person is pregnant or breastfeeding),
- elevated levels of cholesterol, sugar and a type of fat known as triglycerides,
- elevated levels of sugar in your urine,
- increased appetite,
- dizziness,
- a movement disorder that makes it hard for you to stay still known as akathisia. It causes an urge to move that you can't control. You might need to fidget all the time, walk in place, or cross and uncross your legs.
- shaking, slow movement, impaired speech or muscle stiffness,
- a decrease in the amount of white blood cells (leucocytes) in your body, known as leukopenia,
- a decrease of a certain type of white blood cell (neutrophils) in your body, known as neutropenia,
- impairment of voluntary movement,
- orthostatic hypotension, which is a fall in blood pressure when you stand up too quickly from a sitting or lying position and is associated with dizziness, increased heartbeat and in some patients a temporary loss of consciousness,
- anticholinergic effects, such as constipation or dry mouth,
- elevations of certain enzymes in your liver (ALT, AST),
- rash,
- abnormal physical weakness, feeling tired or a lack of energy,
- fever,
- joint pain,
- increased levels of alkaline phosphatase, gamma glutamyltransferase, uric acid and creatinine phosphokinase in your body,
- swelling of the body
- erectile dysfunction in males,
- decreased libido in males and females.

Less frequent side effects:
- abnormally low levels of platelets in your blood,
- hypersensitivity (allergic) reactions,
- development or worsening of diabetes,
- abnormal low body temperature,
- seizures,
- uncontrollable contraction of the muscles,
- involuntary, repetitive body movements which may include grimacing, stick out the tongue or smacking the lips,
- memory loss,
- difficulty in speaking normally,
- stuttering,
- uncontrollable urge to move your legs (Restless Legs Syndrome),
- high fever, muscle stiffness, altered mental status, irregular pulse or blood pressure, increased heartbeat or irregular heartbeat or unusually high sweating for no reason (neuroleptic malignant syndrome),
- withdrawal symptoms such as sweating, diarrhoea, excessive drooling from the mouth, anxiety, agitation, nausea, vomiting, the inability to sleep and involuntary shaking,
- decreased heartbeat,
- a heart rhythm disorder that can potentially cause fast, chaotic heartbeats,
- increased heartbeat,
- the formation of blood clots,
- bleeding from the nose,
- bloating and swelling in the belly area,
- inflammation of the pancreas,
- inflammation of the liver,
- sensitivity to sunlight,
- hair loss,
- flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen on blood tests and an increase in a type of white blood cells (eosinophilia). This is known as Drug reaction with eosinophilia and systemic symptoms or DRESS,
- breakdown of muscle tissue that releases a damaging protein into the blood that damages the kidneys,
- loss of bladder control,
- difficulty in passing urine or trouble starting or maintaining a urine stream,
- drug withdrawal symptoms in newborn babies,
- absence of menstruation,
- breast enlargement in both males and females,
- milky discharge from the nipples (not milk) in females,
- prolonged erection of the penis,
- increased levels of bilirubin the blood.

While taking olanzapine, elderly patients with dementia may suffer from the following:
Frequent side effects:
- seeing things that are not real (hallucinations)
- not walking in a normal manner,
- falls,
- infection in one or both the lungs (pneumonia),
- redness of the skin,
- loss of bladder control,
- a lack of energy and enthusiasm,
- increased body temperature.

Side effects that are observed in patients with drug-induced psychosis associated with Parkinson's disease are the following:
Frequent side effects:
- seeing or hearing things that are not real (hallucinations),
- symptoms like those experienced in Parkinson's disease such as shakes, slow movement, problems with balance, rigidity and difficulty in walking.

When taking olanzapine, patients with bipolar mania that is also taking lithium or valproate, may suffer from the following:
Frequent side effects:
- weight gain,
- increased appetite,
- problems with your speech,
- shaking,
- dry mouth.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects
If you get side effects, talk to your doctor or pharmacist. You can also report side effects to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of PHRENPE.

5. How to store PHRENPE
Store all medicines out of reach of children.
Store at or below 25 °C.
Store in the original package. Protect from light and moisture.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information
What PHRENPE contains
- The active substance is olanzapine. PHRENPE 5 contains 5 mg olanzapine and PHRENPE 10 contains 10 mg olanzapine.
- The other ingredients are mannitol, aspartame, crospovidone (Polyplasdone XL-10), microcrystalline cellulose and magnesium stearate.

What PHRENPE looks like and contents of the pack
PHRENPE 5 mg orodispersible tablets: Yellow coloured, round, flat, bevel edged uncoated tablets with score line on side and debossed "5" on other side.
PHRENPE 10 mg orodispersible tablets: Yellow coloured, round, flat, bevel edged uncoated tablets with score line on side and debossed "10" on other side.
PHRENPE 5 and 10 orodispersible tablets are packed in blisters and the blisters are packed into cartons, containing 10, 14, 28, 30, 35, 50, 56 or 70 tablets per carton. Not all pack sizes may be marketed.

Holder of Certificate of Registration
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South Africa

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PHRENPE 10: 47/2.6.5/0183

Professionele Inligting xxxxxxxx-6513

SKEDULERINGSTATUS: S5

1. NAAM VAN DIE GENEESMIDDEL
PHRENPE 5 (5 mg) en PHRENPE 10 (10 mg) oraal-oplosbare tablette

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
PHRENPE 5 mg oraal-oplosbare tablette
Elke oraal-oplosbare tablet bevat 5 mg olansapien. Bevat versoeter: 1,20 mg aspartaam. Bevat suiker: 41,80 mg mannitol ('n suiker alkohol)
PHRENPE 10 mg oraal-oplosbare tablette
Elke oraal-oplosbare tablet bevat 10 mg olansapien. Bevat versoeter: 2,40 mg aspartaam. Bevat suiker: 83,60 mg mannitol ('n suiker alkohol)
Vir 'n volledige lys van bymiddels, sien afdeling 6.1.

3. DOSEERVORM
Oraal-oplosbare tablette.
PHRENPE 5 mg oraal-oplosbare tablette:
Geelgekleurde, ronde, plat, skuinsgerande, onbedekte tablette met 'n breeklyn aan een kant gedebosseleer met "5" aan ander kant.
PHRENPE 10 mg oraal-oplosbare tablette:
Geelgekleurde, ronde, plat, skuinsgerande, onbedekte tablette met 'n breeklyn aan een kant gedebosseleer met "10" aan ander kant.

4. KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
PHRENPE oraal-oplosbare tablette word aangedui vir die beheer van manifestasies van psigotiese versteurings. Die antipsigotiese doeltreffendheid van olansapien is in gekontroleerde proewe van skisofreniese binne-pasiënte vir die behandeling van positiewe simptome (soos waandenkbeelde, hallusinasies, verwarde denke, vyandigheid en agterdogtigheid) en negatiewe simptome (soos afgestompte gemoed, emosionele en sosiale onttrekking en gebrekkige spraak) vasgestel. Dit word aanbeveel dat pasiënte wat op PHRENPE behandeling reageer voortgaan met die laagste dosis wat remissie handhaaf. Pasiënte moet periodiek geëvalueer word om die nodigheid van instandhoudingsbehandeling te bepaal. PHRENPE word verder aangedui vir die behandeling van 'n akute episode van manie van matige tot erge intensiteit en vir die voorkoming van herhaling van maniese of depressiewe episodes in bipolêre versteurings.

4.2 Posologie en metode van toediening
Posologie
Psigotiese afwykings: PHRENPE oraal-oplosbare tablette moet op 'n daaglikse basis as 'n enkeldosis, sonder inagneming van maaltye, toegedien word. Oor die algemeen moet daar met 'n aanvangsdosis van 5 tot 10 mg per dag begin word, met die teikendosis van 10 mg/dag binne etlike dae na aanvang. Ewewigsvlak vir olansapien word eers na ongeveer een week bereik. Om die evaluasie van effektiwiteit moontlik te maak en om te waak teen newe-effekte moet dosisaanpassings, indien aangedui, met tussenposes van nie minder as een week nie, geskied. Die dosisreeks is 5 mg tot 20 mg per dag. Verhoging van die dosis bo die aanbevole daaglikse dosering van 10 mg word nie sonder toepaslike kliniese ondersoek aanbeveel nie.

Akute manie in bipolêre versteurings: PHRENPE word gewoonlik as 'n daaglikse enkeldosis van 10 mg sonder inagneming van maaltye toegedien. Aanpassings van daaglikse dosering binne die aanbevole 5 mg tot 20 mg per dag, indien aangedui, moet oor die algemeen teen intervalle van nie korter as 24 uur nie, geskied.

Voorkoming van herhaling van episodes in bipolêre versteurings: Die aanbevole aanvangsdosis is 10 mg per dag. In pasiënte wat PHRENPE ontvang vir die behandeling van maniese episodes moet behandeling vir die voorkoming van herhaling, teen dieselfde dosis voortgesit word. Enige vermeerdering tot 'n dosis groter as die aanbevole aanvangsdosis, binne die dosisreeks van 5 mg tot 20 mg per dag, moet deur toepaslike kliniese ondersoek voorafgegaan word. Dosisaanpassings moet oor die algemeen teen intervalle van nie korter as 24 uur nie, geskied. Die veiligheid van dosisse hoër as 20 mg/dag is nie vasgestel nie. Geleidelike vermindering van die dosis moet oorweeg word wanneer PHRENPE behandeling gestaak word (sien afdeling 4.4).

Spesiale pasiëntgroepe
Bejaarde pasiënte
'n Laer aanvangsdosis moet oorweeg word veral as faktore wat die farmakokinetiese opruiming mag verlaag of die farmakodinamiese reaksie op PHRENPE mag versterk, teenwoordig is (sien afdeling 4.4).
Hepatiese inkorting
'n Laer aanvangsdosis van 5 mg moet in pasiënte met lewerinkorting oorweeg word. In pasiënte met matige lewerontoereikendheid (sirrose, Child-Pugh klas A of B) is die aanbevole dosis 5 mg en moet slegs met omsigtigheid verhoog word (sien afdeling 4.4).
Renale inkorting
Dosisaanpassing, gebaseer op die graad van nierontoereikendheid, is nie nodig nie (sien afdeling 5.2).
Pediatriese populasie
Veiligheid en doeltreffendheid in persone jonger as 18 jaar is nie vasgestel nie. PHRENPE word nie vir gebruik in kinders en adolessente onder die ouderdom van 18 jaar aanbeveel nie.

Metode van toediening
PHRENPE oraal-oplosbare tablette moet in die mond geplaas word, waar dit vinnig in speeksel kan oplos sodat dit maklik ingesluk kan word. Verwydering van die heel oraal-oplosbare tablet vanuit die mond is moeilik. Die tablet moet dadelik geneem word wanneer dit uit die verpakking gehaal is aangesien dit maklik breekbaar is. Alternatiewelik kan dit direk voor toediening in 'n glas vol water of ander geskikte vloeistof (lemoensap, appelsap, melk of koffie) opgelos word.

4.3 Kontraïndikasies
- Hipersensitiwiteit vir olansapien (die aktiewe bestanddeel) of vir enige ander hulpstowwe gelys in afdeling 6.1.
- Pasiënte met bekende risiko of nouhoek-gloukoom.
- Kinders en adolessente onder die ouderdom van 18 jaar aangesien veiligheid en doeltreffendheid nog nie vasgestel is nie.

4.4 Spesiale waarskuwings en voorsorg vir gebruik
Tydens antipsigotiese behandeling kan verbetering van die pasiënte se kliniese toestand etlike dae tot weke neem. Pasiënte moet noukeurig tydens hierdie periode gemoniteer word.
Staking van behandeling:
Onttrekkingsreaksies mag ontwikkel, gewoonlik binne 'n week van staking van behandeling met PHRENPE. 'n Cholinergiese sindroom (diaforese, diarree, sialoree, naarheid en braking, angstigheid, agitasie, slaaploosheid en tremor) mag deel van die reaksies uitmaak. Dit word derhalwe aanbeveel dat PHRENPE geleidelik gestaak word. [2,3]
Hiperprolaktinemie:
Olansapien veroorsaak 'n toename in prolaktienvlakke en 'n matige verhoging duur gedurende kroniese toediening voort. 'n Toename in voorkoms van borskliergewasse kan moontlik aan hierdie verhoogde prolaktienvlakke toegeskryf word
Gebruik in bejaarde pasiënte:
Kliniese studies het oor die algemeen nie daarop gedui dat olansapien anders deur bejaarde pasiënte as deur jonger volwassenes verdra word nie. 'n Laer aanvangsdosis moet in die teenwoordigheid van faktore wat die farmakokinetiese opruiming mag verlaag of die farmakodinamiese reaksie op olansapien-bevattende middels soos PHRENPE verhoog, oorweeg word. Aangesien posturale hipotensie per geleentheid tydens kliniese studies in bejaarde pasiënte waargeneem is word dit aanbeveel dat bloeddruklesings periodiek in pasiënte ouer as 65 jaar, geneem word.
Kennis wat betref veiligheid in bejaarde pasiënte met demensie-verwante psigose:
Die effektiwiteit van olansapienbevattende middels soos PHRENPE in bejaarde pasiënte met demensie-verwante psigose is nog nie vasgestel nie. Resultate van plasebo-gekontroleerde kliniese studies in bejaarde pasiënte met demensie-verwante psigose het betekenisvol groter insidensie van dood getoon in pasiënte wie olansapien ontvang het teenoor pasiënte wie plasebo ontvang het (3,5 % tenoor 1,5 %, onderskeidelik). Abnormale gang en val het baie algemeen voorgekom (> 10 %) en urinêre inkontinensie en respiratoriese infeksie was algemeen. 'n Verhoogde insidensie van serebrovaskulêre insidente, insluitend beroerte, is gevind. Risikofaktore wat hierdie pasiëntpopulasie predisponeer vir verhoogde mortaliteit tydens behandeling met PHRENPE sluit ouderdom ≥ 80 jaar, sedasie, gelyktydige gebruik met bensodiasepiene of die teenwoordigheid van pulmonêre kondisies (bv. pneumonie, met of sonder aspirasie) in.
Serebrovaskulêre newe effekte (CVAE), insluitend beroerte, in bejaarde pasiënte met demensie:
Serebrovaskulêre newe effekte (bv. beroerte, kortstondige iskemiese aanval) insluitend sterftes was in olansapienstudies in bejaarde pasiënte met demensie-verwante psigose aangemeld. In plasebo-gekontroleerde studies was daar 'n hoër insidensie van CVAE in pasiënte wie olansapien ontvang het teenoor pasiënte wie plasebo ontvang het (1,3 % teenoor 0,4 % onderskeidelik). Alle pasiënte wat 'n serebrovaskulêre aanval ondervind het, het voorafbestaande risikofaktore gehad wat bekend is dat dit met 'n verhoogde risiko vir CVAE geassosieer word (bv. geskiedenis van 'n vorige CVAE of kortstondige iskemiese aanval, hipertensie en rook van sigarette). Hiérdie pasiënte het meegaande mediese kondisies gehad en/of kombinasie medikasie gebruik wat 'n temporale verhouding met CVAE toon. PHRENPE is nie goedgekeur vir die behandeling van pasiënte met demensie-verwante psigose nie.
Parkinson se siekte:
Weens die geassosieerde verhoging in parkinsons-agtige simptome en hallusinasies asook dat dit in kliniese studies nie meer effektief was as placebo in die behandeling van psigotiese simptome nie, word olansapien nie vir die behandeling van dopamien-agonis-geassosieerde psigose in pasiënte met Parkinson se siekte aanbeveel nie.
Neuroleptiese kwaadaardige sindroom (NMS):
Neuroleptiese kwaadaardige sindroom (NMS) is 'n potensieel lewensgevaarlike kondisie wat met die gebruik van antipsigotiese, medisinale middels soos olansapien, geassosieer word. Simptome van NMS sluit hiperpireksie, spierstyfheid, verandering in geestestoestand en tekens van outonome onstabiliteit (onreëlmatige pols of bloeddruk, tagikardie, diaforese en hartdisritmieë) in. Verhoogde vlakke van kreatinienfosfokinase in serum, mioglobinurie (rabdomiolise) en akute nierversaking mag ook voorkom. PHRENPE moet gestaak word indien enige van die kliniese manifestasies van NMS, of hoë koors sonder addisionele kliniese manifestasies van NMS, waargeneem word.
Hiperglisemie en Diabetes:
Alhoewel ongewoon is behandeling met olansapien geassosieer met hiperglisemie en/of die ontwikkeling of verergering van reeds bestaande diabetes, soms geassosieer met keto-asidose, koma of sterfte. In sommige gevalle is 'n vorige toename in liggaamsgewig gerapporteer, wat 'n predisponerende faktor kan wees. Meting van bloedglukosevlakke aan die begin van die behandeling met PHRENPE, 12 weke na die aanvang van die behandeling, en jaarliks daarna, is aan te beveel. Pasiënte met 'n bestaande diagnose van diabetes mellitus of met risikofaktore vir diabetes mellitus (bv. vetsug, familiegeskiedenis van diabetes) wat met PHRENPE behandeling begin moet gereeld vir verswakking van glukose beheer gemonitor word. Pasiënte wat met PHRENPE behandeling begin moet vir simptome van hiperglisemie, insluitend polidipsie, poliurie, polifagie en swakheid, gemonitor word. Die pasiënt se gewig moet ook gereeld gemonitor word, bv. aan die begin van behandeling met PHRENPE, 4,8 en 12 weke na aanvang van behandeling en kwartaalliks daarna.
Lipiedveranderings:
Pasiënte wat met PHRENPE behandel word, kan ongewenste veranderinge in lipiedvlakke waarneem. Lipiedvlakke van pasiënte wat behandeling met PHRENPE ontvang moet gereeld gemonitor word, bv. aan die begin van behandeling met PHRENPE, 12 weke na die aanvang van behandeling en elke 5 jaar daarna.
Anticholinergiese aktiwiteit:
Aangesien olansapien in vitro anticholinergiese aktiwiteit getoon het, moet PHRENPE met omsigtigheid aan pasiënte met prostaat hipertrofie of verlamde ileus en verwante toestande, voorgeskryf word.
Verhoogde transaminase en hepatiese funksie:
Verbygaande en asimptomatiese stygings in hepatiese aminotransferase, naamlik ALT en/of AST is veral tydens vroeë behandeling met olansapien, algemeen waargeneem. Omsigtigheid is nodig in pasiënte met verhoogde ALT en/of AST vlakke, in pasiënte wat tekens en simptome van lewerinkorting toon, in pasiënte wat met potensieel hepatotoksiese middels behandel word en in pasiënte met voorafbestaande toestande wat met beperkte reserwe van lewerfunksie geassosieer word. In hierdie gevalle moet 'n opvolg gereël word om verdere toetse te doen. 'n Aanvangsdosis van 5 mg moet in pasiënte met matige lewerinkorting (sien afdeling 4.2) oorweeg word. Behandeling met PHRENPE moet gestaak word in gevalle waar hepatitis (insluitend hepatosellulêre, cholestatiese of 'n kombinasie van lewerbesering) gediagnoseer is. In die geval van verhoogde vlakke van alanienaminotransferase (ALT) en / of aspartaataminotransferase (AST) tydens behandeling, moet 'n verlaging in dosis oorweeg word.
Neutropenie:
Omsigtigheid is nodig in pasiënte met lae leukosiet en/of neutrofiel tellings vir welke rede, in pasiënte wat medisyne bekend om neutropenie te veroorsaak word, in pasiënte met 'n geskiedenis van middel-geïnduseerde beenmurgonderdrukking/toksisiteit, in pasiënte met beenmurgonderdrukking veroorsaak word deur gepaardgaande siekte, bestralingsterapie en chemoterapie en in pasiënte met hipereosinofiliese toestande of met mieloproliferatiewe siekte. Neutropenie is algemeen gerapporteer wanneer olansapien en valproaat gelyktydig gebruik word (sien afdeling 4.8).
QT-interval:
Omsigtigheid is nodig wanneer PHRENPE in kombinasie met medisyne wat QTc-interval verhoog, voorgeskryf word (sien afdeling 4.5: Interaksie met ander geneesmiddels en ander vorme van interaksie). Dit is veral nodig by bejaardes, in pasiënte met aangebore lang QT-sindroom, kardiale hipertrofie, kongestiewe hartversaking, hipomagnesemie of hipokalemie.
Trombo-embolisme:
Pasiënte met skisofrenie presenteer dikwels met verworwe risikofaktore vir veneuse trombo-embolisme. Derhalwe moet alle moontlike risikofaktore van veneuse trombo-embolisme geïdentifiseer word (bv. immobilisasie van pasiënte) en voorkomende maatreëls getref word.
Algemene SSS-aktiwiteit:
Gegewe die effekte van olansapien op die primêre sentrale senuweestelsel (SSS) is omsigtigheid nodig wanneer PHRENPE in kombinasie met ander sentraalwerkende medisyne en alkohol, gebruik word. Aangesien olansapien in vitro dopamien-antagonisme vertoon kan PHRENPE die gevolge van direkte en indirekte dopamien-agoniste teenwerk (sien afdeling 4.5).
Konvulsies:
Alhoewel ongewoon is konvulsies tydens behandeling met olansapien by pasiënte aangemeld. In meeste gevalle is 'n geskiedenis van konvulsies of risikofaktore vir konvulsies aangemeld. Derhalwe moet PHRENPE met omsigtigheid gebruik word by pasiënte met 'n geskiedenis van konvulsies of met 'n verlaagde konvulsiedrempel.
Tardiewe diskinesie:
Die insidensie van diskinesie in pasiënte na aanvang van olansapienbehandeling is laag. Die risiko van tardiewe diskinesie verhoog met langdurige gebruik. Indien tekens of simptome van tardiewe diskinesie voorkom by 'n pasiënt wat PHRENPE ontvang, moet 'n dosisvermindering of staking van behandeling oorweeg word. Simptome kan tydelik vererger of selfs ontstaan nadat behandeling gestaak is.
Ortostatiese hipotensie:
PHRENPE kan ortostatiese hipotensie veroorsaak wat met duiseligheid, tagikardie by sommige pasiënte en sinkopie geassosieer word. Dit kan veral tydens aanvang van behandeling voorkom. Weens die risiko van ortostatiese hipotensie met PHRENPE moet omsigtigheid by hartpasiënte gehandhaaf word.
Regulering van liggaamstemperatuur:
Antipsigotiese medisyne kan die liggaam se vermoë om kernliggaamstemperatuur te verlaag ontwrig en hierdeur die risiko vir sonsteek verhoog. Omsigtigheid is nodig in omstandighede wat kan bydra tot 'n verhoogde kernliggaamstemperatuur, soos blootstelling aan uitermatige hitte en strawwe oefening.
Disfagie:
Daar is 'n verhoogde risiko vir aspirasie en esofageale dismotiliteit as antipsigotiese middels gebruik word. PHRENPE moet met omsigtigheid in pasiënte met 'n risiko van aspirasie-pneumonie gebruik word.
Selfmoord:
Noukeurige mediese toesig oor pasiënte met selfmoordneigings word by hoë risiko pasiënte aanbeveel aangesien die moontlikheid van 'n selfmoordpoging inherent aan skisofrenie is.
Skielike hartsterfte:
Skielike hartsterfte is gerapporteer by pasiënte wat olansapien gebruik, soos gesien in na-bemarking verslae.

Pediatriese populasie
PHRENPE word nie vir gebruik in kinders en adolessente onder die ouderdom van 18 jaar aanbeveel nie.
Fenielalanien:
PHRENPE tablette bevat aspartaam wat 'n bron van fenielalanien is. Fenielalanien kan vir mense met fenielketonurie skadelik wees.
Mannitol:
PHRENPE oraal-oplosbare tablette bevat mannitol. Dit mag 'n matige lakserende effek hê.

4.5 Interaksie met ander geneesmiddels en ander vorme van interaksies
Potensiële interaksies wat 'n uitwerking op olansapien kan hê:
Olansapien word deur die iso-ensiem CYP1A2 gemetaboliseer. Substanse wat CYP1A2 spesifiek induseer of inhibeer mag derhalwe die farmakokinetika van olansapien beïnvloed.
Induksie van CYP1A2:
Gelyktydige gebruik van karbamasepien en/of die rook van sigarette kan die metabolisme van olansapien induseer. Hierdie mag tot verlaagde olansapienkonsentrasies lei. Kliniese monitering van die pasiënt word aanbeveel en indien nodig kan 'n verhoging van PHRENPE oorweeg word,.
Inhibisie van CYP1A2:
Daar is gevind dat fluvoksamien, 'n spesifieke CYP1A2 inhibeerder, die metabolisme van olansapien aansienlik kan inhibeer wat tot verhoogde olansapienkonsentrasies sal lei. 'n Laer aanvangsdosis PHRENPE moet oorweeg word by pasiënte wat fluvoksamien of enige ander CYP1A2 inhibeerders soos siprofloksasien, gebruik. 'n Afname in die dosis van PHRENPE moet oorweeg word indien behandeling met 'n inhibeerder van CYP1A2 begin word.
Verminderde biobeskikbaarheid:
Die biobeskikbaarheid van olansapien word met 50 – 60 % verminder wanneer dit saam met geaktiveerde houtskool geneem word. Geaktiveerde houtskool moet minstens 2 ure voor of na PHRENPE geneem word.
Daar is nie gevind dat fluoksetien ('n CYP2D6 inhibeerder), enkele dosisse teensuurmiddel (aluminium, magnesium) of simetidien die farmakokinetika van olansapien beduidend beïnvloed nie.
Die moontlikheid dat olansapien ander medisinale produkte kan beïnvloed:
Olansapien kan die gevolge van direkte en indirekte dopamien-agoniste antagoniseer (sien afdeling 4.4). Olansapien inhibeer nie die hoof CYP450 iso-ensieme in vitro nie. Soos geverifieer deur in vivo studies is geen inhibering van metabolisme vir die volgende stowwe gevind nie: trisikliese antidepressante (wat hoofsaaklik die CYP2D6 weg verteenwoordig), warfarien (CYP2C9), teofillien (CYP1A2) of diasepam (CYP3A4 en 2C19). Olansapien het geen interaksie getoon toe dit gelyktydig met litium of biperideen toegedien is nie. Geen dosisaanpassing is vir valproaat nodig as dit saam met olansapien toegedien word nie. Vanweë die moontlikheid om hipotensie te induseer kan olansapien die effekte van sekere anti-hipertensiewe middels verhoog. Gegewe die uitgebreide kliniese en in vitro studies word daar nie verwag dat olansapien die metabolisme van meeste medisyne sal beïnvloed nie.
Algemene SSS-aktiwiteit:
Weens die primêre uitwerking van olansapien op die sentrale senuweestelsel moet omsigtigheid gebruik word wanneer PHRENPE in kombinasie met ander sentraalwerkende medisyne en alkohol gebruik word (sien afdeling 4.4). Dit word nie aanbeveel om olansapien saam met antiparkinson medisyne te gebruik by pasiënte met Parkinson se siekte en demensie nie (sien afdeling 4.4).
QTc-interval:
Omsigtigheid is nodig wanneer PHRENPE met medisyne wat bekend is dat dit QTc-interval verhoog, voorgeskryf word (sien afdeling 4.4).

4.6 Fertiliteit, swangerskap en borsvoeding
Vrugbaarheid
Pasiënte moet aangeraai word om hul geneesheer te raadpleeg indien hulle tydens behandeling met PHRENPE swanger raak of van plan is om swanger te raak.
Swangerskap
Daar is geen voldoende en goed gekontroleerde studies in swanger vroue nie. Pasgebore babas wat gedurende die derde trimester van die swangerskap aan antipsigotiese medisyne (insluitend olansapien) blootgestel is, is aan 'n risiko van newe-reaksies, insluitend ekstrapiramidale simptome en/of onttrekkingsimptome wat in die erns en duur na die bevalling kan wissel, onderworp. Daar is gevalle van agitasie, hipertonie, hipotonie, bewing, slaperigheid, asemhalingsnood of voedingsversteuring aangemeld. Pasgeborenes moet derhalwe fyn gemonitor word.
Borsvoeding
Olansapien word in menslike borsmelk uitgeskei. Pasiënte moet aangeraai word om nie hul babas te borsvoed tydens behandeling met PHRENPE nie.
Fertiliteit
Die effek op fertiliteit is nog nie vasgestel nie.

4.7 Effek op die vermoë om te bestuur en masjinerie te gebruik
PHRENPE mag slaperigheid en duiseligheid veroorsaak. Pasiënte moet aangeraai word om nie te bestuur of masjinerie te hanteer totdat hulle seker is hoe behandeling met PHRENPE hulle affekteer nie.

4.8 Newe-effekte
a. Opsomming van die veiligheidsprofiel
Die mees gerapporteerde newe-effekte wat met die gebruik van olansapien geassosieer word is slaperigheid, gewigstoename, eosinofilie, verhoogde prolaktien, cholesterol, glukose- en trigliseriedvlakke, glukosurie, verhoogde eetlus, duiseligheid, akatisie, parkinsonisme, leukopenie, neutropenie, diskinesie, ortostatiese hipotensie, anticholinergiese effekte, kortstondige asimptomatiese verhoging van aminotransferase in die lewer, uitslag, astenie, moegheid, pireksie, artralgie, verhoogde alkaliese fosfatase, hoë gamma glutamieltransferase, hoë uriensuur, hoë kreatienfosfokinase en edeem.
b. Getabuleerde opsomming van newe-effekte

MedDRA Sisteem-orgaanklas	Frekwensie	Newe-effek
Bloed- en limfatiese stelsel versteurings	Gereeld	Eosinofilie. Leukopenie. Neutropenie.
	Minder gereeld	Trombositopenie.
Immuunstelsel versteurings	Minder gereeld	Hipersensitiwiteit.
Metabolisme- en voeding versteurings	Gereeld	Gewigstoename. Verhoogde cholesterolvlakke. Verhoogde glukose-vlakke. Verhoogde trigliseriedvlakke. Glukosurie. Verhoogde aptyt.
	Minder gereeld	Ontwikkeling of verergering van diabetes somtyds geassosieer met keto-asidose of koma, insluitend enkele noodlottige gevalle. Hipotermie.
Senuweestelsel versteurings	Gereeld	Slaperigheid. Duiseligheid. Akatisie. Parkinsonisme. Diskinesie
	Minder gereeld	Konvulsies waar in meeste gevalle 'n geskiedenis van konvulsies of risikofaktore vir konvulsies gerapporteer is. Distonie (insluitend okulêre draaiing). Tardiewe diskinesie. Amnesie. Disartrie. Hakkel. Rustelose bene sindroom. Neuroleptiese kwaadaardige sindroom (NMS). Onttrekkingsimptome.
Hartversteurings	Minder gereeld	Bradikardie. QTc verlenging. Ventrikulêre tagikardie/ fibrillasie, skielike dood.
Vaskulêre versteurings	Gereeld	Ortostatiese hipotensie.
	Minder gereeld	Trombo-embolisme (insluitend pulmonêre embolisme en diep veneuse trombose).
Respiratoriese-, torakale- en mediastinale versteurings	Minder gereeld	Epistaxis (Neusbloeding).
Gastro-intestinale versteurings	Gereeld	Ligte, kortstondige anticholinergiese effekte, insluitend hardlywigheid en droë mond.
	Minder gereeld	Abdominale distensie. Pankreatitis.
Hepatobiliêre versteurings	Gereeld	Verbygaande asimptomatiese stygings in hepatiese aminotransferase (ALT, AST), veral tydens vroeë behandeling.
	Minder gereeld	Hepatitis (insluitend hepatosellulêre, cholestatiese of gemengde lewerskade).
Vel en subkutane weefsel versteurings	Gereeld	Uitslag.
	Minder gereeld	Fotosensitiwiteitsreaksie. Alopesie.
	Frekwensie onbekend	Geneesmiddelreaksie met eosinofilie en sistemiese simptome (DRESS).
Skeletspier en bindweefsel versteurings	Gereeld	Artralgie.
	Minder gereeld	Rabdomiolise.
Renale en urinêre versteurings	Minder gereeld	Urinêre inkontinensie, urinêre retensie. Urinêre huiwering.
Swangerskap, puerperium en perinatale toestande	Frekwensie onbekend	Neonatale onttrekkingsindroom.
Voortplantingsisteem- en borsversteurings	Gereeld	Erektiele disfunksie by mans. Verlaagde libido by mans en vroue.
	Minder gereeld	Amenoree. Borsvergroting. Galaktorree by vroue. Ginekomastie/borsvergroting by mans. Priapisme.
Algemene versteurings en toestande by die toedieningsplek	Gereeld	Astenie. Moegheid. Edeem. Pireksie.
Ondersoeke	Gereeld	Verhoogde plasmaprolaktienvlakke. Verhoogde alkaliese fosfatase. Hoë kreatienfosfokinase. Hoë gamma-glutamieltransferase. Hoë uriensuur.
	Minder gereeld	Verhoogde totale bilirubien

c. Beskrywing van spesifieke nadelige reaksies
Geleidelike vermindering van dosis moet oorweeg word wanneer PHRENPE gestaak word (sien afdeling 4.4). Skielike staking van behandeling met PHRENPE kan tot akute simptome soos sweet, diarree, oormatige speekselafskeiding, angs, agitasie, naarheid, braking, slapeloosheid en bewing lei. Behandeling met PHRENPE moet derhalwe geleidelik gestaak word.
d. Ander spesiale pasiëntgroepe
Die onderstaande tabel is 'n opsomming van newe-effekte waargeneem in bejaarde pasiënte met Alzheimertipe demensie wat olansapien ontvang:

MedDRA Sisteem-orgaanklas	Frekwensie	Newe-effek
Psigiatriese versteurings	Gereeld	Visuele hallusinasies.
Senuweestelsel versteurings	Gereeld	Abnormale gang. Val.
Respiratoriese-, torakale- en mediastinale versteurings	Gereeld	Pneumonie.
Vel en subkutane weefsel versteurings	Gereeld	Eriteem.
Renale en urinêre versteurings	Gereeld	Urinêre inkontinensie.
Algemene versteurings en toestande by die toedieningsplek	Gereeld	Letargie.
Ondersoeke	Gereeld	Verhoogde liggaamstemperatuur.

Die onderstaande tabel is 'n opsomming van newe-effekte waargeneem in pasiënte met medikasie-geïnduseerde (dopamien-agonis) psigose geassosieer met Parkinson se siekte:

MedDRA Sisteem-orgaanklas	Frekwensie	Newe-effek
Psigiatriese versteurings	Gereeld	Hallusinasies.
Senuweestelsel versteurings	Gereeld	Parkinson simptomatologie.

Die onderstaande tabel is 'n opsomming van newe-effekte waargeneem in pasiënte met bipolêre manie wat olansapien in kombinasie met litium of valproaat ontvang:

MedDRA Sisteem-orgaanklas	Frekwensie	Newe-effek
Metabolisme en voedingversteurings	Gereeld	Gewigstoename. Verhoogde aptyt.
Senuweestelsel versteurings	Gereeld	Spraakversteuring. Bewing.
Gastro-intestinale versteurings	Gereeld	Droë mond.

Rapportering van vermoedelike nadelige reaksies:
Dit is belangrik om vermoedelike newe-effekte wat waargeneem word nadat die medisyne goedgekeur is, te rapporteer. Dit laat volgehoue monitering van voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike newe-effekte aan SAHPRA te rapporteer via die "6.04 Adverse Drug Reaction Reporting Form", wat aanlyn by SAHPRA se publikasies gevind kan word: https://www.sahpra.org.za/Publications/Index/8

4.9 Oordosering
Tekens en simptome:
Baie algemene simptome wat met olansapienoordosering (> 10 % insidensie) gerapporteer is sluit tagikardie, agitasie/aggressiwiteit, disartrie, verskeie ekstrapiramidale simptome en verlaagde vlak van bewussyn wat wissel van sedasie tot koma, in. Ander beduidende mediese gevolge van olansapienoordosering sluit delirium, konvulsies, koma, moontlike neuroleptiese kwaadaardige sindroom, asemhalingsonderdrukking, aspirasie, hipertensie of hipotensie, hartaritmieë (< 2 % van oordosisgevalle) en hart-long-stilstand, in. Noodlottige gevolge is gerapporteer vir akute oordosisse so laag as 450 mg, maar oorlewing is ook gerapporteer na akute oordosis van 1 500 mg orale olansapien.
Behandeling:
Die moontlikheid van meervoudige geneesmiddelbetrokkenheid moet oorweeg word. In geval van akute oordosering moet 'n lugweg bewerkstellig en instandgehou word en voldoende oksigenering en ventilasie verseker word. Die moontlikheid van obtundasie, konvulsies of distoniese reaksies van die kop en nek wat oordosering volg kan met geïnduseerde braking 'n risiko van aspirasie inhou. Kardiovaskulêre monitering moet onmiddellik begin word en moet volgehoue elektrokardiografiese monitering om moontlike aritmieë te bespeur, insluit. Daar is geen spesifieke teenmiddel vir PHRENPE nie, gevolglik moet toepaslike simptomatiese en ondersteunende behandeling toegepas word. Hipotensie en sirkulêre ineenstorting moet met toepaslike maatreëls soos intraveneuse vloeistowwe en/of simpatomimetiese middels, behandel word. Aangesien β-stimulasie hipotensie kan vererger deur die daarstelling van 'n olansapien-geïnduseerde α-blokkade moet epinefrien, dopamien of ander simpatomimetiese middels met β-agonis-aktiwiteit nie gebruik word nie. Noukeurige mediese toesig en monitering moet voortduur totdat die pasiënt herstel het.

5. FARMAKOLOGIESE EIENSKAPPE
5.1 Farmakodinamiese eienskappe
A 2.6.5 Kalmeermiddels - diverse strukture
Farmakoterapeutiese groep: psigoleptika, diasepiene, oksasepiene, tiasepiene en oksepiene, ATC-kode N05A H03. Olansapien is 'n atipiese antipsigotiese, antimaniese en gemoedstabiliserende middel wat 'n breë farmakologiese profiel oor verskeie reseptorsisteme heen toon. Olansapien het getoon dat dit affiniteit het vir die volgende reseptore: serotonien (5HT2A/2C, 5HT3 en 5HT6), dopamien (D1, D2, D3, D4 en D5), cholinergiese muskarienreseptore (M1-M5), α1-adrenergiese en histamien H1-reseptore. Verdere studies (elektrofisiologiese studies) toon ook dat daar selektiewe wisselwerking tussen olansapien en die mesolimbiese stelsel plaasvind, sonder beduidende wisselwerking met die ekstrapiramidale stelsel. Olansapien verminder 'n gekondisioneerde ontwykingsrespons, 'n toets wat gebruik word om moontlike antipsigotiese aktiwiteit aan te dui, teen dosisse wat laer is as dié wat katalepsie veroorsaak. Katalepsie is 'n toets wat gebruik word om motoriese newe-effekte aan te dui. Olansapien verhoog die reaksie in 'n 'anksiolitiese toets'. In 'n enkel orale dosis van 10 mg Positron-Emissie Tomografie (PET) studie in gesonde vrywilligers het olansapien 'n hoër reseptorbesetting vir die 5HT2A reseptor as die dopamien D2-reseptor getoon. Olansapien se antagonisme van die muskarienreseptore (M1-M5) kan die anticholinergiese effekte daarvan verklaar. Die antagonisme van die histamien H1-reseptore kan die slaperigheid wat ervaar is verklaar en die antagonisme van die adrenergiese α1-reseptore kan die ortostatiese hipotensie wat met hierdie medisyne waargeneem is verklaar.

5.2 Farmakokinetiese eienskappe
Absorpsie
Na orale toediening word olansapien goed geabsorbeer en absorpsie word nie deur kos geaffekteer nie. Piek plasmakonsentrasies word binne 5 tot 8 ure bereik.
Verspreiding
Olansapien is hoofsaaklik aan albumien en α1-suurglikoproteïen gebind. Die plasma-proteïenbinding van olansapien was ongeveer 93 % oor die konsentrasiereeks van ongeveer 7 tot ongeveer 1000 ng/ml.
Biotransformasie
Olansapien word in die lewer via konjugatiewe en oksidatiewe weë gemetaboliseer. Die hoof sirkulerende metaboliet is 10-N-glukoronied en beweeg nie deur die bloedbreinskans nie. Sitokroom P450-CYP1A2 en sitokroom P450-CYP2D6 dra tot die vorming van die N-desmetiel en 2-hidroksimetielmetaboliete by. Beide hierdie metaboliete toon aansienlik minder in vivo farmakologiese aktiwiteit. Die oorheersende farmakologiese aktiwiteit is afkomstig van olansapien, die moederverbinding.
Eliminasie
Gebaseer op resultate van studies wat na orale toediening gedoen is het die eliminasie-halfleeftyd van olansapien in gesonde proefpersone op grond van ouderdom en geslag gewissel:

	< 65 jaar	≥ 65 jaar
Mans	29 ure	49 ure
Vroue	39 ure	55 ure

Gebaseer op resultate van studies wat gedoen is in gesonde ouer persone (65 jaar en ouer) teenoor nie-bejaarde persone was die gemiddelde eliminasiehalfleeftyd verleng en is plasma-opruiming verminder:

	Bejaardes (≥ 65 jaar)	Nie-bejaardes
Eliminasiehalfleeftyd	51,8 ure	33,8 ure
Plasma-opruiming	17,5 l/uur	18,2 l/uur

Omsigtigheid is nodig tydens die dosering van bejaarde persone, veral as daar ander faktore is wat 'n bydraende invloed op die geneesmiddel metabolisme en/of farmakodinamiese sensitiwiteit kan hê. Gebaseer op resultate van studies in vroulike teenoor manlike proefpersone was die gemiddelde eliminasie-halfleeftyd ietwat verleng en plasma-opruiming verminder:

	Vroue	Mans
Eliminasiehalfleeftyd	36,7 ure	32,3 ure
Plasma-opruiming	18,9 l/uur	27,3 l/uur

Olansapien in die dosisreeks van 5 - 20 mg toon 'n vergelykbare veiligheidsprofiel wanneer vroue met mans vergelyk word.

Spesiale pasiëntgroepe
Renale inkorting:
Daar is geen beduidende verskil in gemiddelde eliminasiehalfleeftyd of plasma-opruiming in pasiënte met nierversaking (kreatinienopruiming < 10 ml/min) teenoor gesonde pasiënte nie:

	Renale inkorting (< 10 ml/min)	Gesond
Eliminasiehalfleeftyd	37,7 ure	32,4 ure
Plasma-opruiming	21,2 l/uur	25,0 l/uur

Dosisaanpassing gebaseer op die graad van renale inkorting is nie nodig nie. Daarbenewens word olansapien nie deur hemodialise verwyder nie. Die effek van renale inkorting op die eliminasie van metaboliete is nie bestudeer nie.

Hepatiese inkorting:
Gebaseer op resultate van studies het persone met ligte tot matige hepatiese disfunksie effens verhoogde sistemiese opruiming en vinniger eliminasiehalfleeftyd in vergelyking met proefpersone met geen hepatiese disfunksie nie.
Rook:
By proefpersone wat rook en nie rook nie (mans en vroue) is die gemiddelde eliminasiehalfleeftyd verleng en plasma-opruiming verminder:

	Nie-rokers	Rokers
Eliminasiehalfleeftyd	38,6 ure	30,4 ure
Plasma-opruiming	18,6 l/uur	27,7 l/uur

Plasma-opruiming van olansapien is laer in bejaarde teenoor jong proefpersone, in vroue teenoor mans en by nie-rokers teenoor rokers. Die impak van ouderdom, geslag of rook op plasma-opruiming van olansapien asook halfleeftyd is egter in vergelyking met die algehele wisselvalligheid tussen individue, klein.
Hematologiese toksisiteit:
Gebaseer op resultate van studies in muise en rotte is geen bewyse van beenmurgsitotoksisiteit gevind nie.
Reproduktiewe toksisiteit:
Gebaseer op resultate van studies in muise en rotte is gevind dat olansapien geen teratogeniese effekte het nie.
Mutagenisiteit:
In 'n volledige reeks standaardtoetse, wat bakteriële mutasietoetse en soogdiertoetse in vitro en in vivo insluit, is gevind dat olansapien nie mutagenies of klastogenies is nie.
Karsinogenisiteit:
Gebaseer op resultate van studies in muise en rotte is gevind dat olansapien nie karsinogenies is nie.

6. FARMASEUTIESE BESONDERHEDE
6.1 Lys van hulpstowwe
Mannitol, Aspartaam, Crospovidone (Polyplasdone XL-10), Mikrokristallyne sellulose, Magnesiumstearaat.

6.2 Onverenigbaarheid
Nie van toepassing nie.

6.3 Rakleeftyd
3 jaar

6.4 Spesiale voorsorgmaatreëls tydens berging
Bewaar teen of benede 25 °C.
Bewaar in die oorspronklike verpakking. Beskerm teen lig en vogtigheid.

6.5 Aard en inhoud van die houer
PHRENPE 5 oraal-oplosbare tablette is beskikbaar in Alu/Alu stulpstroke (gewone aluminiumfoelie en koudgevormde OPA/Alu/PVC foelie) en aftrekbare Alu/Alu stulpstroke (stulpstroke met koudgevormde stulpfoelie [CFB] en aftrekbare papier-gesteunde aluminiumfoelie) in kartonne van 10, 14, 28, 30, 35, 50, 56 of 70 tablette per karton.
Nie alle pakgroottes word bemark nie.
PHRENPE 10 oraal-oplosbare tablette is beskikbaar in Alu/Alu stulpstroke (gewone aluminiumfoelie en koudgevormde OPA/Alu/PVC foelie) en aftrekbare Alu/Alu stulpstroke (stulpstroke met koudgevormde stulpfoelie [CFB] en aftrekbare papier-gesteunde aluminiumfoelie) in kartonne van 10, 14, 28, 30, 35, 50, 56 of 70 tablette per karton.
Nie alle pakgroottes word bemark nie.

6.6 Spesiale voorsorg vir die wegdoening van 'n gebruikte medisyne of afvalmateriaal van die medisyne en ander hantering
Geen spesiale voorsorgmaatreëls.

7. HOUER VAN DIE REGISTRASIESERTIFIKAAT
Trinity Pharma (Pty) Ltd.
16de Straat 106, Gebou 2, Midrand, Johannesburg, 1686, Suid-Afrika.

8. REGISTRASIENOMMER(S)
PHRENPE 5: 47/2.6.5/0182
PHRENPE 10: 47/2.6.5/0183

9. DATUM VAN DIE EERSTE GOEDKEURING/MAGTIGING / HERNUWING VAN DIE GOEDKEURING/MAGTIGING
Datum van eerste goedkeuring: 06 April 2021

10. DATUM VAN DIE HERSIENING VAN DIE TEKS
N.A

Pasiëntinligtingsblad

SKEDULERINGSTATUS: S5

PHRENPE 5 mg oraal-oplosbare tablette
PHRENPE 10 mg oraal-oplosbare tablette
Olansapien
PHRENPE 5 bevat versoeter: 1,20 mg aspartaam
PHRENPE 5 bevat suiker: 41,80 mg mannitol
PHRENPE 10 bevat versoeter: 2,40 mg aspartaam
PHRENPE 10 bevat suiker: 83,60 mg mannitol

Lees die hele pamflet sorgvuldig deur voordat u PHRENPE begin gebruik
- Hou hierdie pamflet. U mag dit dalk later weer moet lees.
- Indien u enige verdere vrae het, vra u dokter, apteker, verpleegster of ander gesondheidsorgverskaffer.
- PHRENPE is vir u persoonlik voorgeskryf en u moet nie u medisyne met ander mense deel nie. Dit kan skadelik wees vir hulle, selfs al is hul simptome dieselfde as u simptome.

Wat in hierdie pamflet is
1. Wat PHRENPE is en waarvoor dit gebruik word
2. Wat u moet weet voordat u PHRENPE gebruik
3. Hoe om PHRENPE te gebruik / te neem
4. Moontlike newe-effekte
5. Hoe om PHRENPE te stoor
6. Inhoud van die houer en ander inligting

1. Wat PHRENPE is en waarvoor dit gebruik word
PHRENPE bevat 'n aktiewe bestanddeel wat olansapien genoem word. PHRENPE dien as 'n antipsigotiese, antimaniese en gemoedstabiliseerder en word gebruik om die volgende toestande te behandel:
- Voorkoms van psigotiese versteurings soos skisofrenie.
- Akute episodes van matige of ernstige maniese episodes.
- Voorkoming van herverskyning van maniese of depressiewe episodes van bipolêre versteurings.

2. Wat u moet weet voordat u PHRENPE neem
Moet nie PHRENPE neem:
- Indien u hipersensitief (allergies) vir olansapien of enige van die ander bestanddele van PHRENPE is (gelys in afdeling 6).
- Indien u 'n risiko het om nouhoek-gloukoom ('n siekte waar die drukking in u oog verhoog) te ontwikkel of dit onderlede het.
- Indien u jonger as die ouderdom van 18 jaar is.

Waarskuwings en voorsorgmaatreëls
- U dokter sal u gedurende die beginfase van behandeling monitor om te sien of die medisyne vir u werk.
- Behandeling met PHRENPE moet geleidelik gestaak word deur u dosis te verminder. As die behandeling skielik gestaak word, kan u simptome soos sweet, diarree, oormatige kwyl vanuit die mond, angs, agitasie, naarheid, braking, die onvermoë om te slaap en onwillekeurige skudding ervaar.
- PHRENPE verhoog die vlakke van prolaktien in u bloed (prolaktien is 'n hormoon wat die liggaam instruksie gee om borsmelk te produseer wanneer iemand swanger is of borsvoed). Dit kan u kans om borskanker te ontwikkel, verhoog.
- Die vlakke van vet in u bloed kan verander wanneer u PHRENPE gebruik. U dokter moet hierdie vlakke gereeld monitor, byvoorbeeld aan die begin van die behandeling, na 12 weke en elke 5 jaar daarna.
- 'n Toestand wat bekend staan as tardiewe diskinesie (onwillekeurige, herhalende liggaamsbewegings, wat 'n verdraaiing van u gesig, tong uitsteek of lippe klap kan insluit) kan voorkom as u PHRENPE vir 'n lang tyd gebruik. As dit gebeur moet u dokter u PHRENPE dosis verlaag of dit staak. Hierdie simptome kan tydelik verdwyn of selfs voorkom nadat die behandeling gestaak is.
- Die gebruik van PHRENPE kan 'n toestand wat bekend staan as ortostatiese hipotensie veroorsaak ('n daling in bloeddruk as u te vinnig uit 'n sit- of lê-posisie opstaan en gaan gepaard met duiseligheid, verhoogde hartklop en by sommige pasiënte 'n tydelike verlies aan bewussyn), veral tydens die begin van die behandeling. Omsigtigheid is nodig by pasiënte met hartprobleme, indien u 65 jaar of ouer is moet u bloeddruk gereeld gemeet word.

Wees veral versigtig met PHRENPE:
- indien u medisyne gebruik om 'n siekte genaamd Parkinson se siekte, te behandel. Die simptome wat u normaalweg van Parkinson se siekte kry, sal vererger.
- indien u enige van die volgende simptome ontwikkel:
  - hoë koors,
  - spier styfheid,
  - veranderde geestestoestand,
  - onreëlmatige polsslag of bloeddruk,
  - verhoogde hartklop of onreëlmatige hartklop of
  - oormatig sweet vir geen rede nie

  Hierdie simptome kan daarop dui dat u 'n lewensbedreigende toestand het wat as Neuroleptiese Kwaadaardige Sindroom bekend staan.
  Praat dadelik met u dokter as u van mening is dat u een van die bogenoemde simptome ervaar, selfs al het u vir geen rede nie slegs hoë koors.
  U behandeling met PHRENPE moet onmiddellik gestaak word.
- indien u suikersiekte het, aangesien die gebruik van PHRENPE u bloedsuikervlakke kan verhoog en dit sal u diabetes vererger.
  Terwyl u PHRENPE gebruik kan u diabetes ontwikkel indien u oorgewig is of as u 'n familiegeskiedenis van diabetes mellitus het. U dokter moet u bloedsuikervlakke noukeurig aan die begin van behandeling, na 12 weke en dan een keer per jaar daarna, monitor. Wanneer u PHRENPE begin gebruik moet u dadelik u dokter spreek as u een van die volgende simptome ontwikkel, aangesien dit simptome kan wees wat met diabetes verband hou:
  - oormatige dors,
  - passering van abnormaal hoë volume uriene,
  - oormatig eet of oormatige aptyt, of
  - swakheid.
- indien u meegedeel is dat u demensie-verwante psigose en/of gedragsversteurings het en u:
  - ouer as 65 jaar is,
  - moeilik voedsel of vloeistowwe sluk,
  - ander medisyne gebruik wat sedasie veroorsaak,
  - ondervoed of ontwater is,
  - probleme met u longe het, byvoorbeeld longontsteking,
  - ook 'n groep medisyne bekend as bensodiasepiene (gebruik vir die behandeling van angs) gebruik
- indien u 'n vergrote prostaat of 'n obstruksie van ingewande as gevolg van verlamming van intestinale spiere, het.
- indien u lewerskade het of behandel word met ander medisyne wat u lewer kan benadeel.

U dokter moet gereeld toetse doen om vas te stel of u lewer aangetas word terwyl u PHRENPE neem. U behandeling met PHRENPE moet gestaak word indien u hepatitis (ontsteking van die lewer) ontwikkel.
- indien daar vir u gesê is dat u om welke rede lae vlakke van witbloedselle het.
- indien u medisyne ontvang wat 'n toestand veroorsaak waar witbloedselvlakke in u bloed verlaag (ook neutropenie genoem).
- indien u 'n geskiedenis het van dwelm-geïnduseerde beenmurgdepressie of beenmurgdepressie het wat deur 'n verwante siekte veroorsaak word.
- indien u bestralingsterapie of chemoterapie ontvang (terapie wat gebruik word vir die behandeling van kanker).
- indien daar vir u gesê is dat u hoë vlakke van 'n sekere soort witbloedsel in u bloed het (eosinofiele) of 'n afwyking het waar u bloedmurg te veel abnormale rooibloedselle, witbloedselle of bloedplaatjies produseer wat in u bloed versamel (mieloproliferatiewe siekte).
- indien u ook 'n medisyne gebruik wat bekend staan as valproaat (wat gebruik word vir die behandeling van epilepsie), aangesien dit tot neutropenie kan lei.
- indien u ook medisyne gebruik wat u QT-interval kan verhoog en u:
  - 65 jaar of ouer is,
  - aangebore lang QT-sindroom het ('n versteuring in hartritme wat moontlik vinnige, chaotiese hartklop kan veroorsaak),
  - 'n vergrote hart het,
  - kongestiewe hartversaking het,
  - lae vlakke van magnesium of kalium in u bloed het.
- indien u moontlike risikofaktore het, soos om vir lang tydperke geïmmobiliseer te word, wat kan lei tot 'n veneuse trombo-embolisme.
- wanneer u ook ander sentraalwerkende medisyne en alkohol gebruik.
- indien u 'n geskiedenis van konvulsies (aanvalle) het of risikofaktore het wat tot konvulsies (aanvalle) kan lei.
- indien u van plan is om strawwe oefening te doen of blootgestel gaan word aan uitermatige hitte, aangesien u liggaam se vermoë om kernliggaamstemperatuur te verlaag, belemmer kan word. Dit kan lei tot sonsteek.
- omdat daar 'n verhoogde risiko is vir die inaseming van voedsel, vloeistowwe, speeksel of braaksel in die lugweë en in beweging van die slukderm verminderd is.
- indien u selfdoodneigings het. U moet fyn gemonitor word.
- indien u probleme met u hart het.

Kinders en adolessente
PHRENPE word nie aanbeveel vir gebruik by kinders en adolessente jonger as 18 jaar nie.

Ander medisyne en PHRENPE
Noem altyd aan u gesondheidsorgverskaffer indien u enige ander medisyne neem (dit sluit alle komplimentêre of tradisionele medisyne in).
U moet veral u geneesheer inlig indien u enige van die volgende medisyne gebruik of onlangs gebruik het, en u gebruik ook PHRENPE:
- Karbamasepien – 'n verhoging van u PHRENPE dosis mag nodig wees.
- U sal moontlik ook u dosis PHRENPE moet verhoog indien u sigarette rook.
- Fluvoksamien en/of siprofloksasien – 'n laer aanvangsdosis van PHRENPE moet oorweeg word.
- Geaktiveerde houtskool - die konsentrasie PHRENPE in u bloed word met 50 – 60 % verminder indien dit saam met geaktiveerde houtskool geneem word. Neem geaktiveerde houtskool minstens 2 uur voordat u PHRENPE neem.
- Medisyne vir Parkinson se siekte – PHRENPE mag die uitwerking van hierdie medisyne verlaag.
- Sekere medisyne wat gebruik word om hoë bloeddruk te behandel - PHRENPE kan die uitwerking van hierdie medisyne verhoog, wat daartoe kan lei dat pasiënte baie lae bloeddruk ervaar
- Ander sentraalwerkende medisyne en alkohol.

Dit word nie aanbeveel om PHRENPE saam met anti-Parkinson-medisyne te gebruik by pasiënte met Parkinson se siekte en demensie nie. Omsigtigheid is nodig wanneer PHRENPE saam met medisyne wat bekend is dat dit QT-intervalle verhoog, voorgeskryf word.

PHRENPE met kos, drank en alkohol
PHRENPE kan met of sonder kos geneem word.
PHRENPE kan saam met water of enige ander geskikte vloeistof soos lemoensap, appelsap, melk of koffie geneem word. U kan u PHRENPE in hierdie vloeistowwe oplos voordat u dit inneem, aangesien dit oraal-oplosbare tablette is.
PHRENPE moet nie saam met alkohol geneem word nie.
Swangerskap en borsvoeding
Raadpleeg u dokter, apteker of ander gesondheidsorgverskaffer vir advies voordat u hierdie medisyne gebruik indien u swanger is of borsvoed, vermoed dat u swanger is of van plan is om swanger te word. Die volgende simptome kan by pasgebore babas voorkom waar moeders PHRENPE gedurende hul derde trimester van die swangerskap gebruik het: agitasie, spierstyfheid en/of swakheid, skudding, slaperigheid, asemhalingsprobleme en probleme met voeding. As u baba een van hierdie simptome ontwikkel, moet u moontlik u dokter kontak. U moet nie PHRENPE neem as u u baba borsvoed nie aangesien klein hoeveelhede olansapien in borsmelk mag voorkom. U moet nie u baba borsvoed terwyl u PHRENPE gebruik nie.
Bestuur en gebruik van masjiene
PHRENPE kan slaperigheid en duiseligheid veroorsaak. Dit is dus raadsaam om nie te bestuur of masjiene te gebruik voordat u weet hoe PHRENPE u sal beïnvloed nie. Dit is nie altyd moontlik om te voorspel in watter mate PHRENPE die daaglikse aktiwiteite van 'n pasiënt kan beïnvloed nie. Pasiënte moet toesien dat hulle nie aan bogenoemde aktiwiteite deelneem nie, totdat hulle bewus is van die mate waartoe PHRENPE hulle affekteer.
PHRENPE bevat aspartaam
Pasiënte wat nie fenielalanien kan inneem nie moet ook PHRENPE gebruik nie aangesien dit aspartaam bevat wat 'n bron van fenielalanien is. Dit kan skadelik wees vir pasiënte met fenielketonurie.
PHRENPE bevat mannitol
PHRENPE oraal-oplosbare tablette bevat mannitol. Dit kan 'n ligte lakserende effek hê.

3. Hoe om PHRENPE te neem
Moet nie medisyne wat vir u voorgeskryf is, met enige ander persoon deel nie. Gebruik altyd PHRENPE presies soos u dokter gesê het. Raadpleeg u dokter of apteker indien u onseker is. Die veiligheid van dosisse hoër as 20 mg per dag is nie vasgestel nie.

PHRENPE kan met of sonder kos geneem word. PHRENPE oraal-oplosbare tablette moet dadelik geneem word wanneer dit uit die verpakking gehaal is aangesien dit maklik breekbaar is. PHRENPE oraal-oplosbare tablette moet in die mond geplaas word, waar dit vinnig in speeksel kan oplos sodat dit maklik ingesluk kan word. Alternatiewelik kan dit direk in 'n vol glas water, lemoensap, appelsap, koffie of melk opgelos word. Drink dit dadelik.

Vir gebruik in psigotiese versteurings:
Die aanvangsdosis is gewoonlik 5 tot 10 mg per dag (een maal per dag skedule). Die teikendosis is 10 mg/dag binne etlike dae na aanvang. Om te waak teen newe-effekte en om te bepaal of die medisyne reg werk moet die dosis van PHRENPE nie aangepas word voor een week verby is nie. Die dosisreeks is 5 mg tot 20 mg per dag. Die verhoging van die dosis bo die gewone daaglikse dosis van 10 mg word slegs aanbeveel na toepaslike kliniese assessering plaasgevind het.

Vir die gebruik in akute manie in bipolêre versteurings:
Die gewone aanvangsdosis is 10 mg per dag (eenmaal per dag skedule). Dosisaanpassings binne die dosisreeks van 5 mg tot 20 mg per dag, indien aangedui, moet gewoonlik met tussenposes van minstens 24 uur plaasvind.

Vir die voorkoming van herhaling in bipolêre versteurings:
Die aanbevole aanvangsdosis is 10 mg per dag. As u PHRENPE ontvang het vir die behandeling van maniese episodes moet u voortgaan gaan met dieselfde dosis om te voorkom dat dit weer plaasvind. 'n Verhoging tot 'n dosis hoër as die aanbevole aanvangsdosis, binne die dosisreeks 5 mg tot 20 mg per dag, word slegs na toepaslike kliniese assessering aanbeveel en moet gewoonlik met tussenposes van minstens 24 uur plaasvind. PHRENPE word nie vir gebruik in kinders en adolessente onder die ouderdom van 18 jaar aanbeveel nie. U dokter sal u inlig hoe lank u behandeling met PHRENPE sal duur. Behandeling met PHRENPE moet geleidelik gestaak word deur u dosis geleidelik oor tyd te verminder. Moenie die behandeling voortydig staak nie want u kan simptome soos sweet, diarree, oormatige kwyl vanuit die mond, angs, agitasie, naarheid, braking, onvermoë om te slaap en onwillekeurige skud ervaar. Vra u dokter of apteker indien u onder die indruk is dat die effek van PHRENPE te sterk of te swak is.

Indien u meer PHRENPE neem as wat u moet
Raadpleeg u dokter of apteker in geval van oordosering. As geeneen beskikbaar is nie, kontak die naaste hospitaal of gifsentrum. Sommige van die simptome wat u mag ervaar indien u meer PHRENPE geneem het as wat u moet sluit in:
- verhoogde hartklop,
- angstig voel of aggressief is,
- probleme om normaal te praat,
- verskillende ekstrapiramidale simptome wat skud, sluwe spraak, onbeheerbare of onwillekeurige beweging insluit,
- verlaagde vlak van bewussyn, wat kan wissel van gesedeerd wees tot 'n koma,
- verwarde denke en verminderde bewustheid van die omgewing (delirium),
- stuipe (stuiptrekkings),
- moontlike kwaadaardige neuroleptiese sindroom (simptome sluit in: hoë koors, spierstyfheid, veranderde geestestoestand, onreëlmatige pols of bloeddruk, verhoogde hartklop of onreëlmatige hartklop, uitermatige sweet sonder rede),
- probleme met asemhaling,
- verhoogde risiko om voedsel, vloeistowwe, speeksel of braaksel in die lugweë in te asem,
- verhoogde of verlaagde bloeddruk,
- onreëlmatige hartklop (te stadig of te vinnig),
- hartaanval.

Indien u vergeet om PHRENPE te neem
Moenie twee dosisse gelyktydig neem om die vergete dosis op te maak nie. As u 'n dosis van PHRENPE mis, neem dit sodra u dit onthou.

Indien u ophou om PHRENPE te neem
Behandeling met PHRENPE moet geleidelik gestaak word deur u dosis geleidelik oor tyd te verminder. As die behandeling skielik gestaak word kan u simptome soos sweet, diarree, oormatige kwyl vanuit die mond, angs, agitasie, naarheid, braking, onvermoë om te slaap en onwillekeurige skud ervaar.

4. Moontlik newe-effekte
PHRENPE kan newe-effekte hê.
Nie alle newe-effekte wat vir PHRENPE aangemeld is, is by hierdie pamflet ingesluit nie. As u algemene gesondheid vererger of as u enige ongewenste reaksie ervaar tydens die gebruik van PHRENPE, raadpleeg u gesondheidsorgverskaffer vir advies.

As enige van die volgende gebeur, staak die gebruik van PHRENPE en kontak u dokter onmiddellik of gaan na die ongevalle-afdeling by u naaste hospitaal:
- swelling van die hande, voete, enkels, gesig, lippe mond of keel, wat moontlike probleme met asemhaling of sluk kan veroorsaak,
- uitslag of jeuk,
- floutes.

Hierdie is baie ernstige newe-effekte. As u dit ondervind, het u moontlik 'n ernstige reaksie op PHRENPE gehad. U mag dalk dringende mediese hulp of hospitalisasie benodig.
Stel u dokter in kennis indien u enige van die volgende opmerk:
Volwassenes:
Newe-effekte wat gereeld voorkom:
- slaperigheid,
- gewigstoename,
- 'n toename in 'n sekere soort witbloedsel (eosinofiele) in u liggaam, bekend as eosinofilie,
- verhoogde vlakke van prolaktien (prolaktien is 'n hormoon wat die liggaam die instruksie gee om borsmelk te produseer wanneer iemand swanger is of borsvoed),
- verhoogde vlakke van cholesterol, suiker en 'n tipe vet wat as trigliseriede bekend staan,
- verhoogde vlakke van suiker in u uriene,
- verhoogde eetlus,
- duiseligheid,
- 'n bewegingsversteuring wat dit vir u moeilik maak om stil te staan, bekend as akatisie. Dit veroorsaak 'n drang om te beweeg wat u nie kan beheer nie. U moet dalk heeltyd vroetel, op die plek loop of u bene kruis en weet uitmekaar kruis,
- skudding, stadige beweging, verswakte spraak of spierstyfheid,
- 'n afname in die hoeveelheid witbloedselle (leukosiete) in u liggaam, bekend as leukopenie,
- 'n afname in 'n sekere soort witbloedsel (neutrofiele) in u liggaam, bekend as neutropenie,
- belemmering van vrywillige beweging,
- ortostatiese hipotensie, dit is 'n val in bloeddruk as u te vinnig uit 'n sit- of lê-posisie opstaan en gaan gepaard met duiseligheid, verhoogde hartklop en by sommige pasiënte 'n tydelike verlies aan bewussyn,
- anticholinergiese effekte, soos hardlywigheid of droë mond,
- verhogings van sekere ensieme in u lewer (ALT, AST),
- uitslag,
- abnormale fisiese swakheid, moegheid of gebrek aan energie,
- koors,
- gewrigspyn,
- verhoogde vlakke van alkaliese fosfatase, gamma glutamieltransferase, uriensuur en kreatinienfosfokinase in u liggaam,
- swelling van die liggaam,
- erektiele disfunksie by mans,
- verlaagde libido by mans en vroue.

Newe-effekte wat minder gereeld voorkom:
- abnormale lae vlakke van bloedplaatjies in u bloed,
- hipersensitiwiteit (allergiese) reaksies,
- ontwikkeling of verergering van diabetes,
- abnormale lae liggaamstemperatuur,
- aanvalle,
- onbeheerbare sametrekking van spiere,
- onwillekeurige, herhalende liggaamsbewegings wat kan insluit verdraaiing, tong uitsteek of lippe klap,
- geheueverlies,
- probleme om normaal te praat,
- hakkel,
- onbeheerbare drang om jou bene te beweeg (Rustelose Bene Sindroom),
- hoë koors, spierstyfheid, veranderde geestestoestand, onreëlmatige pols of bloeddruk, verhoogde hartklop of onreëlmatige hartklop of uitermatige sweet sonder enige rede (neuroleptiese kwaadaardige sindroom),
- onttrekkingsimptome soos sweet, diarree, oormatige kwyl vanuit die mond, angs, agitasie, naarheid, braking, die onvermoë om te slaap en onwillekeurige skud,
- verlaagde hartklop,
- 'n versteuring in hartritme wat moontlik vinnige, chaotiese hartklop kan veroorsaak,
- verhoogde hartklop,
- die vorming van bloedklonte,
- bloeding vanuit die neus,
- opgeblasenheid en swelling in die buik-area,
- ontsteking van die pankreas,
- ontsteking van die lewer,
- sensitiwiteit vir sonlig,
- haarverlies,
- Griepagtige simptome met 'n uitslag in die gesig en dan met 'n uitgebreide uitslag, hoë temperatuur, vergrote limfknope, verhoogde vlakke van lewerensieme wat gesien word tydens bloedtoetse en 'n toename in 'n soort witbloedsel (eosinofilie). Dit staan bekend as Geneesmiddelreaksie met eosinofilie en sistemiese simptome of DRESS,
- afbreek van spierweefsel wat 'n skadelike proteïen in die bloed vrystel wat die niere beskadig,
- verlies aan blaasbeheer,
- probleme met urinering of probleme met die begin of instandhouding van 'n uriene straal,
- onttrekkingsimptome by pasgebore babas,
- afwesigheid van menstruasie,
- borsvergroting by mans en vroue,
- melkagtige afskeiding van die tepels (nie melk nie) by vroue,
- langdurige ereksie van die penis,
- verhoogde vlakke van bilirubien in die bloed.

Bejaarde pasiënte met demensie kan tydens die gebruik van olansapien aan die volgende ly:
Newe-effekte wat gereeld voorkom:
- om dinge te sien wat nie waar is nie (hallusinasies),
- abnormale manier van loop,
- val,
- infeksie in een of beide longe (longontsteking),
- rooiheid van die vel,
- verlies aan blaasbeheer,
- 'n gebrek aan energie en entoesiasme,
- verhoogde liggaamstemperatuur.

Newe-effekte wat waargeneem word by pasiënte met dwelm-geïnduseerde psigose wat verband hou met die Parkinson se siekte, is die volgende:
Newe-effekte wat gereeld voorkom:
- dinge sien of hoor wat nie waar is nie (hallusinasies),
- simptome soos dié wat ondervind word met die Parkinson se siekte, soos skud, stadige beweging, probleme met balans, styfheid en moeite om te loop.

Wanneer olansapien gebruik word, kan pasiënte met bipolêre manie wat ook litium of valproaat inneem, aan die volgende ly:
Newe-effekte wat gereeld voorkom:
- gewigstoename,
- verhoogde eetlus,
- probleme met u toespraak,
- skud,
- droë mond.

Stel u dokter of apteker in kennis as u newe-effekte opmerk wat nie in hierdie pamflet genoem word nie.

Aanmelding van newe-effekte
Praat met u dokter, apteker of verpleegster as u newe-effekte ervaar. U kan ook newe-effekte aan SAHPRA rapporteer via die "6.04 Adverse Drug Reaction Reporting Form", wat aanlyn gevind word onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8. Deur newe-effekte aan te meld, kan u help om meer inligting in te win oor die veiligheid van PHRENPE.

5. Hoe om PHRENPE te stoor
Stoor alle medisyne buite bereik van kinders. Stoor teen of benede 25 °C. Stoor in die oorspronklike houer. Beskerm teen lig en vogtigheid. Neem alle ongebruikte medisyne na u apteker terug. Moet nie ongebruikte medisyne in dreine of riooltstelsels wegdoen nie (bv. toilette).

6. Inhoud van die pak en ander inligting
Wat PHRENPE bevat
- Die aktiewe bestanddeel is olansapien. PHRENPE 5 bevat 5 mg olansapien en PHRENPE 10 bevat 10 mg olansapien.
- Die ander bestanddele is mannitol, aspartaam, crospovidone (Polyplasdone XL-10), mikrokristallyne sellulose en magnesiumstearaat.

Hoe PHRENPE lyk en die inhoud van die pak
PHRENPE 5 mg oraal-oplosbare tablette: Geelgekleurde, ronde, plat, skuinsgerande, onbedekte tablette met 'n breeklyn aan een kant gedebosseleer met "5" aan ander kant.
PHRENPE 10 mg oraal-oplosbare tablette: Geelgekleurde, ronde, plat, skuinsgerande, onbedekte tablette met 'n breeklyn aan een kant gedebosseleer met "10" aan ander kant.
PHRENPE 5 en 10 oraal-oplosbare tablette is beskikbaar in stulpstroke en die stulpstroke is verpak in kartonne van 10, 14, 28, 30, 35, 50, 56 of 70 tablette per karton. Nie alle pakgroottes word bemark nie.

Houer van Registrasiesertifikaat
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