SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Olangem OD 20

2. Qualitative and quantitative composition
Each tablet contains 20 mg Olanzapine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Orodispersible Tablets

Description: Yellow coloured, circular, flat faced bevelled edge tablets, debossed with 'C' on one side and '54' on the other side.

4. Clinical particulars
4.1 Therapeutic indications
Adults
Olanzapine is indicated for the treatment of schizophrenia. Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is indicated for the treatment of moderate to severe manic episode. In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder.

4.2 Posology and method of administration
Adults
Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.

Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in combination therapy.

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

During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20 mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours.

Olanzapine can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine. Olanzapine Orodispersible tablets should be placed in the mouth, where it will be rapidly dispersed in saliva, so it can be easily swallowed. Removal of the intact Orodispersible tablet from the mouth is difficult. Since the Orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice, milk or coffee) immediately before administration.

Olanzapine Orodispersible tablet is bioequivalent to Olanzapine tablets is bioequivalent to Olanzapine tablets, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as Olanzapine tablets. Olanzapine Orodispersible tablets may be used as an alternative to Olanzapine tablets.

Special populations
Paediatric population
Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short term studies of adolescent patients than in studies of adult patients.

Elderly
A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant.

Renal and/or hepatic impairment
A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.

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

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

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

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

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.

Dementia-related psychosis and/or behavioural disturbances

Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident.

The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines.

Parkinson's disease

The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended.

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome is a potentially life-threatening condition associated with antipsychotic medicinal products. If a patient develops signs and symptoms indicative of Neuroleptic Malignant Syndrome, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.

Hyperglycaemia and diabetes

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported uncommonly, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor.

Appropriate clinical monitoring is advisable. Patients treated with any antipsychotic medicines, including olanzapine, should be observed for signs and symptoms of Hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipid alterations

Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic medicines, including Olanzapine Orodispersible tablets, should be monitored regularly for lipids.

Anticholinergic activity

Olanzapine in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions.

Hepatic function

Transient, asymptomatic elevations of hepatic aminotransferases, ALT, AST have been seen commonly, especially in early treatment.
Caution should be exercised and follow-up organised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicines. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

Neutropenia
Caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly.

Discontinuation of treatment
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely (≥0.01% and <0.1%) when olanzapine is stopped abruptly.

QT interval
When olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Thromboembolism
Temporal association of olanzapine treatment and venous thromboembolism has been reported uncommonly (≥ 0.1% and < 1%). A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g., immobilisation of patients, should be identified and preventive measures undertaken.

General CNS activity
Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting medicines and alcohol. As it exhibits *in vitro* dopamine antagonism, olanzapine may antagonize the effects of direct and indirect dopamine agonists.

Seizures
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur uncommonly in patients when treated with olanzapine.

Tardive Dyskinesia
The risk of tardive dyskinesia increases with long term exposure, and therefore if signs or symptoms of tardive dyskinesia appear in a patient on olanzapine, a dose reduction or

discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Postural hypotension

Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. It is recommended that blood pressure is measured periodically in patients over 65 years.

Sudden cardiac death

The risk of presumed sudden cardiac death in patients treated with olanzapine was approximately twice the risk in patients not using antipsychotics.

Paediatric population

Olanzapine is not indicated for use in the treatment of children and adolescents. Studies in patients aged 13-17 years showed various adverse reactions, including weight gain, changes in metabolic parameters and increases in prolactin levels.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Potential interactions affecting olanzapine

Since olanzapine is metabolised by CYP1A2, substances that can specifically induce or inhibit this isoenzyme may affect the pharmacokinetics of olanzapine.

Induction of CYP1A2

The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary.

Inhibition of CYP1A2

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

Decreased bioavailability

Activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60% and should be taken at least 2 hours before or after olanzapine. Fluoxetine (a CYP2D6 inhibitor), single doses of antacid (aluminium, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.

Potential for olanzapine to affect other medicinal products

Olanzapine may antagonise the effects of direct and indirect dopamine agonists. Olanzapine does not inhibit the main CYP450 isoenzymes *in vitro* (e.g., 1A2, 2D6, 2C9, 2C19, 3A4). Thus, no particular interaction is expected as verified through *in vivo* studies where no inhibition of metabolism of the following active substances was found: tricyclic

antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19).
Olanzapine showed no interaction when co-administered with lithium or biperiden. Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.

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

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

4.6 Fertility, pregnancy and lactation
Pregnancy
There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. Nevertheless, because human experience is limited, olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

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

Breast-feeding
In breast-feeding, healthy women, olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady state was estimated to be 1.8% of the maternal olanzapine dose (mg/kg). Patients should be advised not to breast-feed an infant if they are taking olanzapine.

Fertility
Effects on fertility are unknown.

4.7 Effects on ability to drive and use machines
Olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

4.8 Undesirable effects
Adults
The most frequently (seen in ≥ 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels, glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia, dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases, rash, asthenia, fatigue, pyrexia, arthralgia, increased alkaline

phosphatase, high gamma glutamyltransferase, high uric acid, high creatine phosphokinase and oedema.

Tabulated list of adverse reactions

The following table lists the adverse reactions. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥10%), common (≥ 1% and <10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and to 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

Very common	Common	Uncommon	Not known
Blood and the lymphatic system disorders			
	Eosinophilia	Leukopenia Neutropenia	Thrombocytopenia
Immune system disorders			
			Allergic reaction
Metabolism and nutrition disorders			
Weight gain	Elevated cholesterol levels Elevated glucose levels Elevated triglyceride levels Glucosuria Increased appetite		Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases Hypothermia
Nervous system disorders			
Somnolence	Dizziness Akathisia Parkinsonism Dyskinesia		Seizures where in most cases a history of seizures or risk factors for seizures were reported Neuroleptic malignant syndrome Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms
Cardiac disorders			
	Bradycardia QTc prolongation		Ventricular tachycardia/fibrillation, sudden death
Vascular disorders			
	Orthostatic hypotension		Thromboembolism (including pulmonary embolism and deep vein thrombosis)

		Epistaxis	
Gastrointestinal disorders			
	Mild, transient anticholinergic effects including constipation and dry mouth		Pancreatitis
Hepato-biliary disorders			
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)
Skin and subcutaneous tissue disorders			
	Rash		Photosensitivity reaction Alopecia
Musculoskeletal and connective tissue disorders			
			Rhabdomyolysis
Renal and urinary disorders			
		Urinary incontinence	Urinary hesitation
Reproductive system and breast disorders			
			Priapism
General disorders and administration site conditions			
	Asthenia Fatigue Oedema		
Investigations			
Elevated plasma prolactin levels		High creatine phosphokinase Increased total bilirubin	Increased alkaline phosphatase

<u>Additional information on special populations</u>

Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

Olanzapine administered with lithium or valproate resulted in increased levels (≥10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also

reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of body weight occurs.

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

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥10%), common (≥ 1% and < 10%).

Metabolism and nutrition disorders *Very common:* Weight gain, elevated triglyceride levels, increased appetite. *Common:* Elevated cholesterol levels
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth.
Hepato-biliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST.
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16] .

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are asked to report any suspected adverse reactions to the marketing authorization holder or if available via the national reporting system (See details below);

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions.*

4.9 Overdose
Signs and symptoms
Very common symptoms in overdose (>10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (<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 2 g of oral olanzapine.

Management of Overdose
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e., gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Psycholeptics, diazepines, oxazepines thiazepines and oxepines. ATC code: N05A H03.

Pharmacodynamic Properties
Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

Olanzapine exhibited a range of receptor affinities for serotonin 5 HT2A/2C, 5 HT3, 5 HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors m1-m5; α1 adrenergic; and histamine H1 receptors.

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. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.

Paediatric population
During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin were greater in adolescents than in adults.

5.2 Pharmacokinetic properties
Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food. Absolute oral bioavailability relative to intravenous administration has not been determined. Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier.

Cytochromes P450-CYP1A2 and P540-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites. The pre-dominant pharmacologic activity is

from the parent, olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. 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.

The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1,000 ng/ml. Olanzapine is bound pre-dominantly to albumin and α1-acid glycoprotein. The pharmacokinetics of olanzapine is similar between adolescents and adults.

The average olanzapine exposure was approximately 27% higher in adolescents. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers.

Such factors possibly contribute to the higher average exposure observed in adolescents.

5.3 Preclinical safety data

Acute (single-dose) toxicity

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

Repeated-dose toxicity

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

Haematologic toxicity

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

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

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

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

6. Pharmaceutical particulars

6.1 List of excipients
Mannitol (SD 200)
Mannitol (Mannitol 35)
Polacrilin Potassium
Crospovidone (Type A)
Silica, Colloidal Anhydrous
Aspartame
Cellulose, Microcrystalline (grade-112)
Sodium Stearyl Fumarate
Art Pineapple (FL SD # 883)

6.2 Incompatibilities
None known.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30°C. Store in an original pack in order to protect from light and moisture.

6.5 Nature and contents of container
Cold form Aluminium foils blister pack, 4 x 7's.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
Aurobindo Pharma Limited
Plot No.2, Maitrivihar, Ameerpet, Hyderabad,
Zip Code: 500 038, Telangana State.
India.

8. Marketing authorisation number(s)
TAN 20 HM 0423

9. Date of first authorisation/renewal of the authorisation
25/09/2020

10. Date of revision of the text