Date of submission: 04/03/2022
Post registration amendment (0006)

AMENDED PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ALONZA 2,5 / 5 / 10 mg (film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ALONZA 2,5 mg: Each film coated tablet contains 2,5 mg olanzapine.

ALONZA 5 mg: Each film coated tablet contains 5 mg olanzapine.

ALONZA 10 mg: Each film coated tablet contains 10 mg olanzapine.

Contains sugar: Lactose monohydrate

Each 2,5 mg film coated tablet contains 61,70 mg lactose monohydrate.

Each 5 mg film coated tablet contains 59,20 mg lactose monohydrate.

Each 10 mg film coated tablet contains 118,40 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ALONZA 2,5 mg: White to off-white, round, biconvex, film coated tablets, plain on both sides.

ALONZA 5 mg: White to off-white, round, biconvex, film coated tablets, debossed with ‘O1’ on one side and plain on other side.

ALONZA 10 mg: White to off-white, round, biconvex, film coated tablets, debossed with ‘O3’ on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Initials:

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The antipsychotic efficacy of **ALONZA** was established in controlled trials of schizophrenic in-patients in the treatment of positive symptoms (such as delusions, hallucinations, disordered thinking, hostility and suspiciousness) and negative symptoms (such as blunted effect, emotional and social withdrawal and poverty of speech). It is recommended that responding patients be continued on **ALONZA** at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

ALONZA 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

ALONZA may be taken without regard to food.

Psychotic disorders:

ALONZA should be taken once daily. The recommended starting dose is 5 - 10 mg daily, with a target dose of 10 mg daily 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 of olanzapine would not be achieved for approximately one week of treatment. The dose range is from 5 - 20 mg daily. Increasing the dose over the routine daily dose of 10 mg is only advised after appropriate clinical assessment.

Acute mania in bipolar disorder:

ALONZA should be taken once daily. The starting dose is 10 mg daily. If dosage adjustments are indicated within the dose rang of 5 - 20 mg daily, they should generally occur in intervals not less than 24 hours.

Preventing recurrence in bipolar disorder:

The recommended starting dose is 10 mg daily. Patients who have been receiving **ALONZA** for the treatment of manic episodes should continue treatment at the same dose to prevent recurrence. An increase above the

starting dose in the range of 5 - 20 mg is only recommended after appropriate clinical assessment and should generally not occur in intervals less than 24 hours.

Safety of doses above 20 mg daily have not been established.

The dose should be gradually tapered when discontinuing **ALONZA.**

Special populations

Elderly population

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

Hepatic impairment

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

Renal impairment

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

Paediatric population

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

4.3 Contraindications

ALONZA is contraindicated in the following:

- Hypersensitivity to olanzapine or any other ingredients of **ALONZA** (see section 6.1).
- Known risk of narrow-angle glaucoma.
- Safety and efficacy have not been established in patients under 18 years of age.

4.4 Special warnings and precautions for use

During antipsychotic treatment, imporvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.

Discontinuation reaction:

ALONZA should be gradually discontinued. A discontinuation reaction may occur within a week after discontinuation. This reaction may consist of cholinergic syndrome (diaphoresis, diarrhoea, sialorrhoea, nausea, vomiting, anxiety, agitation, insomnia and tremor).

Hyperprolactinaemia

ALONZA elevates prolactin levels and a modest elevation persists during chronic administration. An increase in mammary gland neoplasms has been found in rodents after chronic administration of antipsychotic medicines and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumours in rodents is unknown.

Neuroleptic malignant syndrome:

Neuroleptic malignant syndrome (NMS) may occur in association with **ALONZA**. NMS is a potentially fatal symptom complex. **ALONZA** should be discontinued if any clinical manifestations of NMS or high fever occur. The clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias), elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

Tardive dyskinesia:

Olanzapine, as contained in **ALONZA** has been associated with treatment emergent dyskinesia. A dose reduction or discontinuation of treatment should be considered if signs or symptoms of tardive dyskinesia occur. The risk of tardive dyskinesia may increase over long term exposure to **ALONZA** and symptoms may temporarily deteriorate or arise when **ALONZA** is discontinued.

Seizures:

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ALONZA should be used with caution in patients with a history of seizures or who have conditions which may lower the seizure threshold.

Transaminase elevations and hepatic impairment:

Transient elevations of liver transaminases (ALT, AST) have been observed. Caution should be used in patients with elevated ALT and/or AST, and in treating patients with hepatic function impairment, pre-existing conditions associated with limited hepatic functional reserve and patients who are being treated with potentially hepatotoxic medicines. Transaminase levels should be assessed periodically in patients with significant hepatic disease. A starting dose of 5 mg should be considered in patients with moderate hepatic impairment. In the event of raised alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels during treatment, a dose reduction should be considered. **ALONZA** should be discontinued in patients who have been diagnosed with hepatitis.

Hyperglycaemia and Diabetes Mellitus:

Hyperglycaemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, have been associated with the use of olanzapine, as contained in **ALONZA**. Patients with diabetes mellitus who are taking **ALONZA** should be monitored regularly for worsening glucose control and patients who have risk factors for developing diabetes mellitus (e.g. family history of diabetes mellitus, obesity) should be monitored for symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia and weakness. Fasting blood glucose testing is recommended in patients who develop symptoms of hyperglycaemia.
In some cases, hyperglycaemia has resolved when olanzapine was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Elderly use:

In clinical studies with olanzapine, in general, there was no indication of any different tolerability of **ALONZA** in the elderly compared to younger adults.

Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, or increase the pharmacodynamic response to **ALONZA**, should lead to consideration of a lower starting dose, as postural hypotension was infrequently observed in the elderly in clinical trials.

Safety experience in elderly patients with dementia-related psychosis:

The safety and efficacy of **ALONZA** in elderly patients with dementia related psychosis have not been established. In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients. Abnormal gait and falls were very common, 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 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

CVAE (e.g. stroke, transient ischaemic attack), including fatalities, have been 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. 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 ischaemic attack, hypertension, cigarette smoking) and presented with concurrent medical conditions and/or concomitant medications having a temporal association with CVAE.

ALONZA is not approved for patients with dementia-related psychosis.

Patients and caregivers should report any signs of cerebrovascular adverse events such as weakness, numbness or problems with speech or vision.

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Patients with Alzheimer's dementia may have an increased risk of aspiration pneumonia or seizures (due to the lowered seizure threshold associated with Alzheimer's disease), with the use of **ALONZA.**

Parkinson's disease

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

Sudden cardiac death

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

QT interval

In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post-baseline in patients with baseline QTcF< 500 msec) were uncommon in patients treated with olanzapine with no significant differences in associated cardiac events compared to placebo. However, caution should be exercised when **ALONZA** is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia

Thromboembolism

Temporal association of olanzapine treatment and venous thromboembolism (VTE) has been reported uncommonly. 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.

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Lipid alterations

Undesirable alterations in lipids have been observed with the use of **ALONZA**. Appropriate clinical monitoring is recommended, especially in dyslipidemic patients and in patients with risk factors for the development of lipids disorders.

Haematology:

Caution should be exercised in patients with low leukocyte and/or neutrophil counts, patients with a history of medicine induced bone marrow depression/toxicity, bone marrow depression caused by concomitant illness, radiation- or chemotherapy, and in patients with hypereosinophilic conditions or myeloproliferative disease.

Dysphagia:

ALONZA should be used with caution in patients who are at risk of developing aspiration pneumonia. Oesophageal dysmotility and aspiration have been associated with olanzapine, as contained in **ALONZA**.

Suicide:

Patients should be closely monitored during early therapy with **ALONZA**, as suicide is an inherent risk in schizophrenia.

Cardiovascular conditions:

Caution is advised in patients with cardiovascular disease (including myocardial infarction or ischemia), unstable heart disease, conduction abnormalities or heart failure, as well as in patients with cerebrovascular disease or other conditions that will predispose the patient to hypotension (including dehydration or hypovolaemia).

ALONZA may exacerbate cardio- and cerebrovascular conditions and increase the risk of orthostatic hypotension.

ALONZA may induce orthostatic hypotension, especially during the initial phases of treatment. Periodic blood pressure measurements are recommended in patients > 65 years of age.

No difference in tolerability have been observed in elderly patients. However, caution is advised in the presence of factors that may be responsible for a decrease in pharmacokinetic clearance or increase in pharmacodynamic response. Consideration of a possible lower starting dose is recommended.

ALONZA may disrupt the ability of the body to reduce core body temperature. Appropriate care is advised when prescribing **ALONZA** to patients who will experience conditions that may contribute to elevations in core body temperature, such as dehydration, exposure to extreme heat or strenuous exercise.

Caution is advised when prescribing **ALONZA** to patients with prostatic enlargement, narrow-angle glaucoma (see section 4.3) or paralytic ileus and related conditions. **ALONZA** exacerbate these conditions due to the cholinergic antagonism by olanzapine.

Carcinogenesis

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

Mutagenesis

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.

Impairment of fertility

In rats, male mating, but not fertility, was impaired. Discontinuance of olanzapine treatment reversed the effect on mating performance. In female rats, oestrus cycles and reproduction parameters were influenced at doses higher than the maximum human dose.

Lactose

ALONZA contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **ALONZA**.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for* ALONZA *to affect other medicinal products:

ALONZA may antagonise the effects of direct and indirect dopamine agonists.

Olanzapine showed little potential to inhibit cytochromes P450-CYP1A2, -CYP2C9, -CYP2C19, -CYP2D6 and -CYP3A4 *in vitro*.

Therefore, **ALONZA** is not expected to interfere with the metabolism of most medicines.

No inhibition of metabolism of tricyclic antidepressant such as imipramine or desipramine (P450-CYP2D6 or P450-CYP3A/1A2), warfarin (P450-CYP2C9), theophylline (P450-CYP1A2), or diazepam (P450-CYP3A4 and P450-CYP2C19) was evident.

Co-administration of **ALONZA** with lithium or biperiden have shown no interaction.

Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant **ALONZA** therapy. Concomitant administration of valproate and **ALONZA** may cause increased risk of neutropenia, tremor, dry mouth, increased appetite and weight gain.

General central nervous system (CNS) activity:

Caution should be exercised in patients who consume alcohol, diazepam or receive other medicinal products that can cause CNS depression. Concomitant therapy with **ALONZA** may have an additive CNS depressive effect and orthostatic hypotension may be potentiated.

Because **ALONZA** exhibits dopamine antagonism *in vitro*, **ALONZA** may antagonise the effects of levodopa and other dopamine agonists.

QT interval:

Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval, especially in the elderly or in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Antihypertensive agents:

ALONZA may enhance the effect of certain antihypertensive agents, as it has the potential to induce hypotension.

Potential for other medicines to affect ALONZA

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

Single doses of antacid (aluminium, magnesium) or cimetidine did not affect the oral bioavailability of olanzapine. However, the concomitant administration of activated charcoal reduced the bioavailability of oral olanzapine by 50 to 60 % and should be taken at least 2 hours before or after olanzapine.

Fluoxetine (60 mg single dose or 60 mg daily for 8 days) in combination with olanzapine (5 mg single dose), causes a mean 16 % increase in the maximum concentration of olanzapine and a mean 16 % decrease in olanzapine clearance. The effect of repeat dosage of olanzapine and higher dosages has not been evaluated. Combination therapy is not advised.

Administration of intramuscular lorazepam (2 mg) one hour after intramuscular olanzapine (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam or total lorazepam. However,

this coadministration of intramuscular lorazepam and intramuscular olanzapine added to the somnolence observed with either medicine alone.

Induction of CYP1A2

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

Inhibition of CYP1A2

Known potent inhibitors of CYP1A2 activity may decrease olanzapine clearance. Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine C_{max} 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 or ketoconazole. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

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

New born infants exposed to **ALONZA** during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery.

There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Lactation

Olanzapine is excreted in breast milk. Patients should be advised not to breastfeed an infant if they are taking **ALONZA**.

Fertility

The effect of olanzapine on fertility in humans is unknown.

4.7 Effects on ability to drive and use machines

ALONZA may cause side effects such as somnolence, hallucinations and visual disturbances. Patients should not drive a vehicle or operate machinery until they know how **ALONZA** affects them.

4.8 Undesirable effects

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Blood and lymphatic system disorders	Frequent	Eosinophilia, leukopenia, neutropenia
	Less frequent	Thrombocytopaenia
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, peripheral oedema

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	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, hallucinations, abnormal gait, falls
	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 leg syndrome, neuroleptic malignant syndrome, discontinuation symptoms
Cardiac disorders	Less frequent	Bradycardia, QTc prolongation Ventricular tachycardia / fibrillation, sudden death
Vascular disorders	Frequent	Orthostatic hypotension, hypotension
	Less frequent	Thromboembolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal disorders	Frequent	Pneumonia
	Less frequent	Epistaxis
Gastrointestinal disorders	Frequent	Mild, transient anticholinergic effects including constipation and dry mouth
	Less frequent	Abdominal distension, pancreatitis

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Hepatobiliary disorders	Frequent	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment
	Less frequent	Hepatitis (including hepatocellular, cholestatic or mixed liver injury)
Skin and subcutaneous tissue disorders	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	Amenorrhoea, breast enlargement, galactorrhoea in females, gynaecomastia / breast enlargement in males, priapism
General disorders and	Frequent	Asthenia, fatigue, oedema, pyrexia

administration site conditions		
Investigations	Frequent	Elevated plasma prolactin levels Increased alkaline phosphatase, high creatine phosphokinase, high gamma glutamyl transferase, high uric acid
	Less frequent	Increased total bilirubin

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals 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

Symptoms:

Symptoms of an overdose with **ALONZA** include tachycardia, agitation or aggressiveness, dysarthria, various extrapyramidal symptoms, reduced level of consciousness (ranging from sedation to coma), delirium, convulsion, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension, hypotension, cardiopulmonary arrest and cardiac dysrhythmias. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of 1500 mg.

Treatment:

There is no specific antidote for **ALONZA**. Treatment should be symptomatic and supportive.

In the event of an overdose, multiple medicine involvement should be considered. The administration of activated charcoal together with a laxative should be considered. Induction of emesis is not recommended. The possibility of obtundation, seizures or dystonic reaction of the head and neck may create a risk of aspiration

with induced emesis. It is important to establish and maintain an airway to ensure adequate oxygenation and ventilation.

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

Do not use epinephrine (adrenaline), 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

Pharmacotherapeutic group: psychotics, diazepines, oxazepines, thiazepines and oxepines, ATC code N05A H03

Pharmacological classification: A 2.6.5 Tranquilisers – miscellaneous structures

Olanzapine is an atypical antipsychotic, antimanic and mood-stabilising agent with an affinity for multiple receptors $5HT_{2A/2C}$, $5HT_3$, $5HT_6$, dopamine D_4, D_3, D_1, D_2, cholinergic muscarinic receptors (m_1 - m_5), α_1-adrenergic and histamine H_1 receptors. Olanzapine selectively interacts with the mesolimbic system without significant interaction with the extrapyramidal system.

In experimental animals, olanzapine reduces a conditioned avoidance response, a test predictive of antipsychotic activity, at doses below those required to produce catalepsy, a test predictive of motor side effects. Olanzapine increases response in an 'anxiolytic' test. In a single dose (10 mg) PET study in healthy volunteers, olanzapine produced higher 5HT2A than dopamine D2 receptor occupancy.

The anticholinergic effects of olanzapine may be explained by the antagonism of olanzapine to muscarinic receptors (m_1 - m_5), the antagonism of histamine H_1 receptors may explain the somnolence while the antagonism of α_1-adrenergic receptors may explain the orthostatic hypotension associated with olanzapine.

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5.2 Pharmacokinetic properties

Absorption:

Olanzapine is well absorbed after oral administration. Absorption is not affected by the concomitant intake of food and peak plasma concentrations are reached within 5 - 8 hours.

Metabolism:

Olanzapine is metabolised by means of glucuronidation or 1A2 mediated oxidation in the liver. The major metabolite is 10-*N*glucoronide, and other metabolites include the *N*-desmethyl and 2-hydroxymethyl metabolites. The olanzapine parent compound is predominantly responsible for pharmacological activity.

Distribution:

Olanzapine is highly protein bound, predominantly to albumin and α1-acid-glycoprotein, at a concentration of 93 % between a concentration range of 7 - 1 000 ng/ml.

Elimination:

Elimination of olanzapine from the plasma may be more rapid than from sites of high lipid content and binding. The mean plasma half-life of olanzapine is 24,2 hours. Age, gender and smoking may substantially affect the pharmacokinetics of olanzapine.

The elimination half-life of olanzapine varies according to gender and age. In patients < 65 years the elimination half-life is 29 hours and 39 hours for men and women respectively, while in patients ≥ 65 years, the elimination half-life is 49 hours and 55 hours respectively. The mean elimination half-life of olanzapine is about 1,5 times greater in the elderly and plasma clearance is higher in smoking patients. Renal impairment does not affect the pharmacokinetics of olanzapine and dosage adjustment is not necessary. Olanzapine is not eliminated through dialysis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ALONZA 2,5 / 5 / 10 mg (film-coated tablet)

Lactose monohydrate

Cellulose Microcrystalline (Flocel 101)

Crospovidone (Polyplasdone XL-10)

Hydroxypropylcellulose (Klucel EXF)

Hydroxypropylcellulose (Klucel EF)

Magnesium Stearate

Seal coating

Hypromellose E5

Film coating

Opadry 13B58802 White

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

Store at or below 25 °C.

Do not remove the tablets from the container until required for use.

KEEP ALL MEDICINES OUT OF REACH AND SIGHT OF CHILDREN.

Do not use the tablets after the expiry date printed on the container.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains and sewerage systems (e.g. toilets).

6.4 Special precautions for storage

This medicine does not contain any special storage conditions.

6.5 Nature and contents of container

Silver aluminium/aluminium blister strips containing 14 tablets.

Pack size: 28 (2 blisters strips x 14 tablets per blister strip).

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ALONZA 2,5 mg: White to off-white, round, biconvex, film coated tablets, plain on both sides.

ALONZA 5 mg: White to off-white, round, biconvex, film coated tablets, debossed with 'O1' on one side and plain on other side.

ALONZA 10 mg: White to off-white, round, biconvex, film coated tablets, debossed with 'O3' on one side and plain on other side.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Tuscany Office Park, Building 2

6 Coombe Place, Rivonia,

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

ALONZA 2,5 mg: 49/2.6.5/0035

ALONZA 5 mg: 49/2.6.5/0036

ALONZA 10 mg: 49/2.6.5/0037

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1 June 2021

10. DATE OF REVISION OF THE TEXT

15 June 2022