APPROVED PACKAGE INSERT FOR ZOLANZ 5 and 10 TABLETS

SCHEDULING STATUS

S5

PROPRIETARY NAMES AND DOSAGE FORMS

ZOLANZ 5 TABLETS (film coated tablets)

ZOLANZ 10 TABLETS (film coated tablets)

COMPOSITION

Active ingredient:

Each tablet contains 5 mg or 10 mg olanzapine respectively.

Inactive ingredients:

Crospovidone, hypromellose, lactose monohydrate, magnesium stearate and Opadry White (containing lecithin, talcum, titanium oxide and xanthan gum).

Contains sugar: lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION

A 2.6.5 Tranquillisers - miscellaneous structures.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Olanzapine is an atypical antipsychotic, antimanic and mood-stabilising agent. Olanzapine exhibits affinity for $5HT_{2A/2C}$, $5HT_3$, $5HT_6$, dopamine D_4, D_3, D_1, D_2, cholinergic muscarinic receptors (M_1 - M_5), α_1-adrenergic and histamine H_1 receptors. The binding and antagonism of muscarinic receptors (M_1 - M_5) may explain the anticholinergic effects of olanzapine, while the antagonism of histamine H_1 receptors may explain the somnolence observed with olanzapine. The induced orthostatic hypotension observed during olanzapine use, is explained by its

antagonism of adrenergic α_1-receptors. Olanzapine selectively interacts with the mesolimbic system without significantly interacting with the extrapyramidal system, indicating that higher doses are required to produce motor side effects compared to the lower doses to yield antipsychotic activity.

Pharmacokinetic properties:

Olanzapine is well absorbed after oral administration, and peak plasma concentrations are reached within 5 to 8 hours. The rate and extent of olanzapine absorption are not affected by food.

Olanzapine is extensively metabolised in the liver primarily by conjugative and oxidative pathways mediated by cytochrome P450 isoenzymes CYP1A2 and to lesser extent CYP2D6. The major metabolite, 10-*N*-glucuronide, does not pass the blood-brain barrier. 4-*N*-desmethyl and 2-hydroxymethyl olanzapine are not pharmacologically active at the plasma levels achieved during normal therapeutic olanzapine dosing. The predominant pharmacological activity is from the parent compound. The elimination half-life of olanzapine is about 1,5 times higher in the elderly (≥ 65 years) than in non-elderly subjects (< 65 years), and it varies in healthy subjects depending on the age and gender as follows:

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

The mean apparent plasma clearance is 25 ℓ per hour. Approximately 57 % of the administered dose of olanzapine is renally excreted (7 % unchanged olanzapine), with 30 % excreted faecally. The pharmacokinetics of olanzapine was similar in patients with severe renal impairment and in patients with normal renal function. No dosage adjustment based upon the degree of renal impairment is therefore required. The effect of renal impairment on the elimination of the metabolites of olanzapine has not been studied.

Olanzapine shows a high protein binding of 93 % primarily to albumin and α_1-acid glycoprotein. The pharmacokinetics are linear over the therapeutic dosage range.

Plasma clearance of olanzapine is higher in smokers with the potential of substantial pharmacokinetic differences in population based on age, gender and smoking. Dosing adjustments may therefore be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine.

INDICATIONS

ZOLANZ TABLETS is indicated for the management of the manifestations of psychotic disorders.

ZOLANZ TABLETS exhibited antipsychotic efficacy in schizophrenic patients in the treatment of positive symptoms (such as delusions, hallucinations, disordered thinking, hostility and suspiciousness) and negative symptoms (such as blunted effect, emotional and social withdrawal, poverty of speech).

ZOLANZ TABLETS is also indicated for:

- The treatment of an acute episode of moderate to severe mania.
- Prevention of the recurrence of manic or depressive episodes of bipolar disorder.

CONTRAINDICATIONS

- Hypersensitivity to olanzapine or any of the other ingredients of **ZOLANZ TABLETS** (see **COMPOSITION**).
- Known risk of narrow-angle glaucoma.
- Safety and efficacy have not yet been established in patients less than 18 years of age.

WARNINGS AND SPECIAL PRECAUTIONS

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

Discontinuation reactions:

ZOLANZ TABLETS treatment should not be stopped abruptly, but be discontinued gradually in view of the discontinuation reactions that may occur. Normally within a week of discontinuing **ZOLANZ TABLETS**, reactions consisting of a cholinergic syndrome (diaphoresis, diarrhoea, sialorrhoea, nausea, vomiting, anxiety, agitation, insomnia and tremor) may occur.

Neuroleptic malignant syndrome (NMS):

NMS is a potentially fatal symptom complex. Cases of NMS have been associated with olanzapine, as in **ZOLANZ TABLETS**, treatment. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include acute renal failure, elevated creatine phosphokinase and myoglobinuria (rhabdomyolysis). Treatment with **ZOLANZ TABLETS** should be discontinued if any of the clinical manifestations of NMS or high fever without additional clinical manifestations of NMS is observed.

Seizures:

ZOLANZ TABLETS 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 infrequently in patients treated with olanzapine. In most of these cases, a history of seizures or risk factor for seizures was reported.

Tardive dyskinesia:

ZOLANZ TABLETS has been associated with a low incidence of treatment emergent dyskinesia. If signs or symptoms of tardive dyskinesia appear in a patient on **ZOLANZ TABLETS**, a dose reduction or discontinuation of treatment should be considered. However, some patients may benefit from continued treatment with **ZOLANZ TABLETS** despite the

presence of this syndrome. The risk of tardive dyskinesia increases with long-term exposure and symptoms can temporarily deteriorate or even arise after discontinuation of treatment.

Hepatic impairment:

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

Transient elevations of liver transaminases (alanine transaminase (ALT), aspartate transaminase (AST)) have been observed. Caution should therefore be exercised in patients with elevated ALT and/or AST. In the event of elevated ALT and/or AST during treatment, follow-up appointments should be organised and dose reduction should be considered. In cases where hepatitis has been diagnosed, **ZOLANZ TABLETS** treatment should be discontinued.

Safety experience in elderly patients with dementia-related psychosis:

In elderly patients with dementia-related psychosis, the efficacy of olanzapine has not been established. Cerebrovascular adverse effects such as stroke and transient ischaemic attacks, including fatalities, have occurred in elderly patients with dementia-related psychosis. Any signs, such as numbness and problems with speech or vision, should be reported. Risk factors that may predispose this patient population to increased mortality when treated with **ZOLANZ TABLETS** include age ≥ 80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration).

ZOLANZ TABLETS is not indicated for the treatment of patients with dementia-related psychosis.

Hyperglycaemia and diabetes mellitus:

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, may occur in diabetic patients using **ZOLANZ TABLETS**. Patients with an

established diagnosis of diabetes mellitus who are started on **ZOLANZ TABLETS** should be monitored regularly for worsening of glucose control. Patients who develop symptoms of hyperglycaemia during treatment with **ZOLANZ TABLETS** should undergo fasting blood glucose testing.

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

Hyperprolactinaemia:

ZOLANZ TABLETS 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 finding prolactin mediated endocrine tumours in rodents is unknown.

Parkinson's disease:

ZOLANZ TABLETS is not recommended for use in patients with Parkinson's disease. The use of **ZOLANZ TABLETS** has been commonly associated with increased parkinsonian symptoms and hallucinations.

Prostatic enlargement, narrow angle glaucoma or paralytic ileus and related conditions:

Due to the anticholinergic activity of olanzapine, caution is advised when prescribing **ZOLANZ TABLETS** for patients with symptomatic prostatic enlargement, narrow-angle glaucoma (see **CONTRAINDICATIONS**) or paralytic ileus and related conditions.

Cardiac conditions:

Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Because of the risk of orthostatic hypotension or bradycardia with **ZOLANZ TABLETS**, caution should be taken in cardiac patients.

Renal impairment:

(See **Pharmacokinetic properties**).

Use in the elderly:

There was no indication of different tolerability of **ZOLANZ TABLETS** in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, or increase the pharmacodynamic response to **ZOLANZ TABLETS**, should lead to consideration of a lower starting dose. It is recommended that blood pressure is measured periodically in patients over 65 years of age.

Orthostatic hypotension:

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

Haematology:

Caution should be exercised when using **ZOLANZ TABLETS**:

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

Body temperature regulation:

Disruption of the ability of the body to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing **ZOLANZ TABLETS** for patients who will be experiencing conditions which may contribute to an elevation in core body temperature.

Dysphagia:

Oesophageal dysmotility and aspiration have been associated with olanzapine. **ZOLANZ TABLETS** should therefore be used with caution in patients at risk for aspiration pneumonia.

Suicide:

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

Effects on ability to drive and use machines:

ZOLANZ TABLETS may cause side effects such as somnolence. Patients should be cautioned about driving a vehicle or operating hazardous machinery, until they are certain that **ZOLANZ TABLETS** therapy does not affect them adversely.

Lactose monohydrate:

ZOLANZ TABLETS contains lactose monohydrate (see **COMPOSITION**). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take **ZOLANZ TABLETS**.

INTERACTIONS

- Central effects of other CNS depressants (including alcohol) may be enhanced by **ZOLANZ TABLETS**.
- As it exhibits *in vitro* dopamine antagonism, **ZOLANZ TABLETS** may antagonise the effects of levodopa and dopamine agonists.

- When **ZOLANZ TABLETS** is given in combination with valproate, neutropenia may be more common. Use with valproate or lithium has been associated with an increased incidence of tremor, dry mouth, increased appetite and weight gain.
- Because of the potential for inducing hypotension, **ZOLANZ TABLETS** may enhance the effects of certain antihypertensive agents.
- Caution should be exercised when **ZOLANZ TABLETS** is given with other medicines that are known to cause QT prolongation, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.
- **ZOLANZ TABLETS** has α_1-adrenergic antagonist activity. Caution should be exercised in patients who receive treatment with medicinal products that can lower blood pressure by mechanisms other than α_1-adrenergic antagonism.

Potential for medicines to affect ZOLANZ TABLETS:

- Single doses of antacid (aluminium, magnesium) or cimetidine did not affect the oral bioavailability of olanzapine.
- 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 in combination with **ZOLANZ TABLETS**, cause an increase in the maximum concentration of olanzapine, and a decrease in olanzapine clearance. The effect of repeat dosage of **ZOLANZ TABLETS** and higher dosages have not been evaluated. Combination therapy is not advised.

Potential cytochrome P450 interactions affecting olanzapine:

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

Induction of CYP1A2:

The metabolism of olanzapine may be induced by concomitant smoking or carbamazepine, omeprazole, or rifampicin therapy causing subsequent slightly to moderately lower plasma levels of **ZOLANZ TABLETS**. Clinical monitoring is recommended and an increase of **ZOLANZ TABLETS** 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 area under the curve (AUC) was 52 % and 108 % respectively in female non-smokers and male smokers. A lower starting dose of **ZOLANZ TABLETS** 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 **ZOLANZ TABLETS** should be considered if treatment with an inhibitor of CYP1A2 is initiated.

Potential for ZOLANZ TABLETS to affect other medicines:

Olanzapine may antagonise the effects of direct and indirect dopamine agonists. In clinical trials with single doses of olanzapine, no inhibition of the metabolism of imipramine, desipramine, warfarin, theophylline or diazepam was evident. Olanzapine shows no interaction when co-administered with biperiden. Olanzapine shows little potential to inhibit cytochromes P450-CYP1A2, -CYP2C9, -CYP2C19, -CYP2D6, and -CYP3A4 in human liver microsomes. Valproate was found to reduce plasma concentrations of olanzapine contained in **ZOLANZ TABLETS**.

PREGNANCY AND LACTATION

Safety of **ZOLANZ TABLETS** during pregnancy and lactation has not been established. Olanzapine is excreted in breast milk. Breastfeeding during treatment with **ZOLANZ TABLETS** is not recommended.

DOSAGE AND DIRECTIONS FOR USE

ZOLANZ TABLETS should be administered once daily with or without food.

Continuation at the lowest dose needed to maintain remission is recommended for responding patients. Periodic reassessment of patients should be performed to determine the need for maintenance treatment.

Psychotic disorders:

The initial dose is 5 to 10 mg per day with a target dose of 10 mg per day within several days. In order to evaluate efficacy and prevent side effects, dosage increases should not be considered before one week of therapy, as steady state levels are achieved in approximately one week. The dose ranges from 5 mg to 20 mg per day as a single daily dose. Increasing the dose over 10 mg per day is advised only after appropriate clinical assessment has been performed.

Acute mania in bipolar disorder:

ZOLANZ TABLETS should be given once daily, with a recommended dosage of 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 of mania in bipolar disorder:

The recommended initial dose is 10 mg per day. For patients who have been receiving **ZOLANZ TABLETS** for treatment of manic episode, continue therapy for preventing recurrence at the same dose. Increasing the dose over 10 mg is advised only after appropriate clinical assessment has been performed and should generally occur at intervals of not less than 24 hours. The safety of doses above 20 mg per day has not been established. Gradual tapering of the dose should be considered when discontinuing **ZOLANZ TABLETS** (see **WARNINGS AND SPECIAL PRECAUTIONS**).

SIDE EFFECTS

Blood and the lymphatic system disorders:

Less frequent: Leucopenia, neutropenia, eosinophilia, agranulocytosis

Frequency unknown: Thrombocytopenia

Immune system disorders:

Frequency unknown: Allergic reaction, anaphylactoid reaction, angioedema, facial oedema

Metabolism and nutrition disorders:

Frequent: Peripheral oedema

Less frequent: Exacerbation of diabetes

Frequency unknown: Glucosuria, diabetic coma, diabetic ketoacidosis, hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia, water intoxication

Psychiatric disorders:

Frequent: Personality disorder, mood or mental changes, amnesia, anxiety, euphoria, hostility, nervousness, hallucinations

Less frequent: Somnolence, apathy, confusion, insomnia, stuttering

Nervous system disorders:

Frequent: Agitation, akathisia, dizziness, parkinsonism, dyskinesia (including buccoglossal syndrome, choreoathetosis), dystonia, residual effects (including movement disorder), myoclonus, twitching, tardive dyskinesia, tremor, syncope

Less frequent: Seizures, headache, speech disorder, paraesthesia, neuroleptic malignant syndrome (see **WARNINGS AND SPECIAL PRECAUTIONS**), abnormal gait, hypertonia

Eye disorders:

Less frequent: Abnormal vision

Frequency unknown: Diplopia

Cardiac disorders:

Less frequent: Bradycardia, tachycardia, QTc prolongation

Frequency unknown: Ventricular extrasystoles, palpitation

Vascular disorders:

Frequent: Orthostatic hypotension, hypertension

Frequency unknown: Venous thromboembolism (including pulmonary embolism and deep vein thrombosis)

Respiratory, thoracic and mediastinal disorders:

Less frequent: Pharyngitis, increased cough, pneumonia

Frequency unknown: Dyspnoea, rhinitis

Gastrointestinal disorders:

Frequent: Constipation, dry mouth, increased appetite

Less frequent: Dyspepsia, abdominal pain, nausea (dose related), vomiting

Frequency unknown: Pancreatitis, increased salivation, thirst

Hepatobiliary disorders:

Less frequent: Hepatitis, jaundice

Skin and subcutaneous tissue disorders:

Less frequent: Rash, acne, dry skin, alopecia, photosensitivity

Frequency unknown: Skin rash, pruritus, urticaria, sweating

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Rhabdomyolysis, joint pain

Renal and urinary disorders:

Less frequent: Urinary incontinence

Reproductive system and breast disorders:

Frequent: Vaginitis, hyperprolactinaemia

Less frequent: Dysmenorrhoea

Frequency unknown: Priapism, menstrual changes, decreased libido, galactorrhoea

General disorders and administrative site conditions:

Frequent: Weight gain, fever, chest pain, flu-like symptoms

Less frequent: Asthenia, weight loss, extremity pain

Frequency unknown: Discontinuation reaction (cholinergic syndrome)

Investigations:

Frequent: Increased prolactin, increased ALT/SGPT, increased AST/SGOT

Less frequent: Increased ALP (alkaline phosphatase), increased bilirubin

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Signs and symptoms:

Very common symptoms reported in **ZOLANZ TABLETS** overdose include tachycardia, agitation, aggressiveness, dysarthria, various extrapyramidal symptoms and reduced level of consciousness, ranging from sedation to coma. Other medically significant sequelae of **ZOLANZ TABLETS** overdose include delirium, convulsion, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac dysrhythmias 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 1 500 mg.

Treatment:

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

There is no specific antidote to **ZOLANZ TABLETS**, 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 (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.

Olanzapine (as in **ZOLANZ TABLETS**) is not removed by haemodialysis.

IDENTIFICATION

ZOLANZ 5 TABLETS: White to off-white, round shaped, biconvex, film coated tablet, debossed with “ZP29” on one side and plain on the other side.

ZOLANZ 10 TABLETS: White to off-white, round shaped, biconvex, film coated tablet, debossed with “ZP31” on one side and plain on the other side.

PRESENTATION

ZOLANZ TABLETS are packed into aluminium/aluminium foil blister strips of 10 tablets each.

Pack sizes of 10 (1 blister strip per outer carton) or 30 (3 blister strips per outer carton).

STORAGE INSTRUCTIONS

Store at or below 25 °C in blister strips.

Protect from light and moisture.

Do not remove from outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

ZOLANZ 5 TABLETS: 43/2.6.5/0666

ZOLANZ 10 TABLETS: 43/2.6.5/0667.

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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