For the use of a Psychiatrist Only

TOLAZ LA

1. Generic Name

Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection

2. Composition

Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection 210mg

TOLAZ LA 210 mg/Vial

Each Combipack Contains:

A. Vial of Olanzapine Pamoate Prolonged Release Powder for Suspension

Each Vial contains:

Olanzapine embonate Monohydrate Ph.Eur

(Olanzapine Pamoate Monohydrate) equivalent to Olanzapine 210 mg

After reconstitution each ml of suspension contains 150mg Olanzapine.

B. Vial of Vehicle 3 ml

Clear, colorless to slight yellow solution contains:

Mannitol I.P.	5.070% w/v
Sodium Carboxymethyl Cellulose I.P.	0.770% w/v
Polysorbate 80 I.P.	0.025% w/v
Hydrochloric acid I.P.	q.s.
Sodium Hydroxide I.P.	q.s.
Water for Injection I.P.	q.s. to 100%

C. One 3ml Disposable Syringe

D. Three 19 gauge, 1.5 inch (38mm) Hypodermic Needles with protection device.

Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection 300mg

TOLAZ LA 300 mg/Vial

Each Combipack Contains:

A. Vial of Olanzapine Pamoate Prolonged Release Powder for Suspension

Each Vial contains:

Olanzapine embonate Monohydrate Ph.Eur

(Olanzapine Pamoate Monohydrate) equivalent to Olanzapine 300 mg

After reconstitution each ml of suspension contains 150mg Olanzapine.

B. Vial of Vehicle 3 ml

Clear, colorless to slight yellow solution contains:

Mannitol I.P.	5.070% w/v
Sodium Carboxymethyl Cellulose I.P.	0.770% w/v
Polysorbate 80 I.P.	0.025% w/v
Hydrochloric acid I.P.	q.s.
Sodium Hydroxide I.P.	q.s.
Water for Injection I.P.	q.s. to 100%

C. One 3ml Disposable Syringe

D. Three 19 gauge, 1.5 inch (38mm) Hypodermic Needles with protection device.

Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection 405mg

TOLAZ LA 405 mg/Vial

Each Combipack Contains:

A. Vial of Olanzapine Pamoate Prolonged Release Powder for Suspension

Each Vial contains:
Olanzapine embonate Monohydrate Ph.Eur
(Olanzapine Pamoate Monohydrate) equivalent to Olanzapine 405 mg
After reconstitution each ml of suspension contains 150mg Olanzapine.
B. Vial of Vehicle 3 ml
Clear, colorless to slight yellow solution contains:

Mannitol I.P.	5.070% w/v
Sodium Carboxymethyl Cellulose I.P.	0.770% w/v
Polysorbate 80 I.P.	0.025% w/v
Hydrochloric acid I.P.	q.s.
Sodium Hydroxide I.P.	q.s.
Water for Injection I.P.	q.s. to 100%

C. One 3ml Disposable Syringe
D. Three 19 gauge, 1.5 inch (38mm) Hypodermic Needles with protection device.

Qualitative and quantitative formula:
Pamoic acid
Dimethyl sulfoxide
Acetone
Mannitol
Sodium Carboxymethyl Cellulose
Polysorbate 80
Hydrochloric acid
Sodium Hydroxide

3. Dosage form and strength
Dosage form: Prolonged Release Powder for Suspension for IM Injection
Strength: 210, 300, 405 mg/Vial

4. Clinical particulars

4.1 Therapeutic indication
For the treatment of Schizophrenia

4.2 Posology and method of administration
Dosage
TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) is intended for deep intramuscular gluteal injection only and should not be administered intravenously or subcutaneously.
Establish tolerability with oral olanzapine prior to initiating treatment.

TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) should be administered by a healthcare professional every 2 to 4 weeks by deep intramuscular gluteal injection using a 19-gauge, 1.5-inch needle.
Following insertion of the needle into the muscle, aspiration should be maintained for several seconds to ensure that no blood is drawn into the syringe. If any blood is aspirated into the syringe, it should be discarded and fresh drug should be prepared using a new convenience kit. The injection should be performed at a steady, continuous pressure. Do not massage the injection site.

TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) is presented as Yellow crystalline powder filled in 5 ml flint glass vials USP type I equivalent to 210, 300, or 405 mg olanzapine per vial. The diluent is a clear colorless to slight yellow mobile solution filled in 3 ml flint glass vials USP type I. The reconstituted suspension will be yellow and opaque.

Dose Selection-The efficacy of TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) has been demonstrated within the range of 150 mg to 300 mg administered every 2 weeks and with 405 mg administered every 4 weeks. Dose recommendations considering oral Olanzapine and TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) are shown in the following Table.

Recommended Dosing for TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) Based on Correspondence to Oral Olanzapine Doses

Target Oral Olanzapine Dose	**Dosing of TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) During the First 8 Weeks**	**Maintenance Dose After 8 Weeks of TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) Treatment**
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

Olanzapine Long Acting Injection doses greater than 405 mg every 4 weeks or 300 mg every 2 weeks have not been evaluated in clinical trials.

Post-Injection Delirium/Sedation Syndrome-During premarketing clinical studies, adverse events that presented with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, were reported in patients following an injection of Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection. Patients should be informed of this risk and how to recognize related symptoms. Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection must be administered in a registered healthcare facility with ready access to emergency response services. After each TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) injection, a healthcare professional must continuously observe the patient at the healthcare facility for at least 3 hours for symptoms consistent with olanzapine overdose, including sedation (ranging from mild in severity to coma) and/or delirium (including confusion, disorientation, agitation, anxiety, and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension, and convulsion. The potential for onset of an event is greatest within the first hour.

The majority of cases have occurred within the first 3 hours after injection; however, the event has occurred after 3 hours. Following the 3-hour observation period, healthcare

professionals must confirm that the patient is alert, oriented, and absent of any signs and symptoms of post-injection delirium/sedation syndrome prior to being released. All patients must be accompanied to their destination upon leaving the facility. For the remainder of the day of each injection, patients should not drive or operate heavy machinery, and should be advised to be vigilant for symptoms of post-injection delirium/sedation syndrome and be able to obtain medical assistance if needed. If post-injection delirium/sedation syndrome is suspected, close medical supervision and monitoring should be instituted in a facility capable of resuscitation.

Dosing in Specific Populations-Tolerance of oral Olanzapine should be established prior to initiating treatment with TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection). The recommended starting dose is TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) 150 mg/4 wks in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine. When indicated, dose escalation should be undertaken with caution in these patients.

Olanzapine Long Acting Injection has not been studied in subjects under 18 years of age.

Maintenance Treatment-Although no controlled studies have been conducted to determine how long patients should be treated with Olanzapine Long Acting Injection, efficacy has been demonstrated over a period of 24 weeks in patients with stabilized schizophrenia. Additionally, oral olanzapine has been shown to be effective in maintenance of treatment response in schizophrenia in longer-term use. Patients should be periodically reassessed to determine the need for continued treatment.

Switching from Other Antipsychotics-There are no systematically collected data to specifically address how to switch patients with schizophrenia from other antipsychotics to Olanzapine Long Acting Injection.

Instructions to Reconstitute and Administer TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection)

For deep intramuscular gluteal injection only. Not to be injected intravenously or subcutaneously.

Step 1: Preparing Materials

Convenience kit includes :

- Vial of TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) powder
- 3-mL vial of diluent
- One 3-mL disposable syringe
- Three 19-gauge, 1.5-inch (38 mm) Hypodermic Needle with protection device.
- For obese patients, a 2-inch (50 mm), 19-gauge or larger needle (not included in convenience kit) may be used for administration.

TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) must be suspended using only the diluent supplied in the convenience kit.

It is recommended that gloves are used when reconstituting, as TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) may be irritating to the skin. Flush with water if contact is made with skin.

Step 2: Determining Reconstitution Volume

Refer to the table below to determine the amount of diluent to be added to powder for reconstitution of each vial strength.

It is important to note that there is more diluent in the vial than is needed to reconstitute.

Dose	Vial Strength	Diluent to Add
150 mg	210 mg	1.3 mL
210 mg	210 mg	1.3 mL
300 mg	300 mg	1.8 mL
405 mg	405 mg	2.3 mL

Step 3: Reconstituting TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection)

Loosen the powder by lightly tapping the vial.

Open the prepackaged Hypodermic Needle with protection device.

Withdraw the pre-determined diluent volume (Step 2) into the syringe.

Inject the diluent into the powder vial.

Withdraw air to equalize the pressure in the vial by pulling back slightly on the plunger in the syringe.

Remove the needle from the vial, holding the vial upright to prevent any loss of material.

Engage the needle safety device.

Pad a hard surface to cushion impact (see Figure 1). Tap the vial firmly and repeatedly on the surface until no powder is visible.

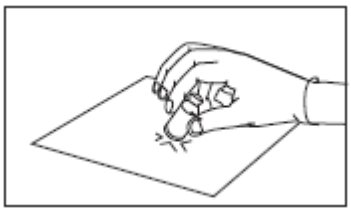

Figure 1: Tap firmly to mix.

Visually check the vial for clumps. Unsuspended powder appears as yellow, dry clumps clinging to the vial. Additional tapping may be required if large clumps remain (see Figure 2).

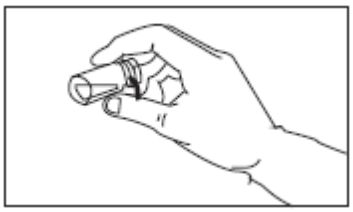

Figure 2: Check for unsuspended powder and repeat tapping if needed.

Shake the vial vigorously until the suspension appears smooth and is consistent in color and texture. The suspended product will be yellow and opaque (see Figure 3).

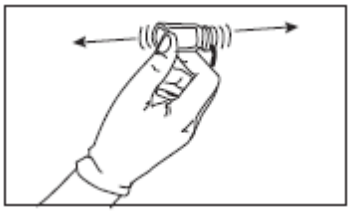

Figure 3: Vigorously shake vial.

If foam forms, let vial stand to allow foam to dissipate.
If the product is not used right away, it should be shaken vigorously to re-suspend. Reconstituted TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection) remains stable for up to 24 hours in the vial.

Step 4: Injecting TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection)

Before administering the injection, confirm there will be someone to accompany the patient after the 3-hour observation period. If this cannot be confirmed, do not give the injection.
Refer to the table below to determine the final volume to inject.

Suspension concentration is 150 mg/mL TOLAZ LA (Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection).

Dose	Final Volume to Inject
150 mg	1 mL
210 mg	1.4 mL
300 mg	2 mL
405 mg	2.7 mL

Attach a new safety needle to the syringe.
Slowly withdraw the desired amount into the syringe.
Some excess product will remain in the vial.
Engage the needle safety device and remove needle from syringe.
For administration, select the 19-gauge, 1.5-inch (38 mm) Hypodermic needle with protection device. For obese patients, a 2-inch (50 mm), 19-gauge or larger needle (not included in convenience kit) may be used. **To help prevent clogging, a 19-gauge or larger needle must be used.**
Attach the new safety needle to the syringe prior to injection. Once the suspension has been removed from the vial, it should be injected immediately.
For deep intramuscular gluteal injection only. Do not inject intravenously or subcutaneously.
Select and prepare a site for injection in the **gluteal** area.
After insertion of the needle into the muscle, **aspirate for several seconds to ensure that no blood appears.** If any blood is drawn into the syringe, discard the syringe and the dose and begin with a new convenience kit. The injection should be performed with steady, continuous pressure.
Do not massage the injection site.
Engage the needle safety device.
Dispose of the vials, needles, and syringe appropriately after injection. The vial is for single-use only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

WARNING: POST-INJECTION DELIRIUM/SEDATION SYNDROME AND INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIARELATED PSYCHOSIS

Post-Injection Delirium/Sedation Syndrome — Adverse events with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of Olanzapine Long acting injection. After each injection, patients must be observed at the healthcare facility by a healthcare professional for at least 3 hours.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Olanzapine Long acting injection is not approved for the treatment of patients with dementia-related psychosis.

Special care must be taken to apply appropriate injection technique to avoid inadvertent intravascular or subcutaneous injection.

Use in patients who are in an acutely agitated or severely psychotic state

TOLAZ LA should not be used to treat patients with schizophrenia who are in an acutely agitated or severely psychotic state such that immediate symptom control is warranted.

Post-injection syndrome

During pre-marketing clinical studies, reactions that presented with signs and symptoms consistent with olanzapine overdose were reported in patients following an injection of TOLAZ LA. These reactions occurred in <0.1% of injections and approximately 2% of patients. Most of these patients have developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsion. In most cases, initial signs and symptoms related to this reaction have appeared within 1 hour following injection, and in all cases full recovery was reported to have occurred within 24 - 72 hours after injection. Reactions occurred rarely (<1 in 1,000 injections) between 1 and 3 hours, and very rarely (<1 in 10,000 injections) after 3 hours. Patients should be advised about this potential risk and the need to be observed for 3 hours in a healthcare facility each time TOLAZ LA is administered. Post-marketing reports of post-injection syndrome since the marketing authorization of TOLAZ LA are generally

consistent with the experience seen in clinical studies.

After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose.

Immediately prior to leaving the healthcare facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. If an overdose is suspected, close medical supervision and monitoring should continue until examination indicates that signs and symptoms have resolved. The 3-hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose.

For the remainder of the day after injection, patients should be advised to be vigilant for signs and symptoms of overdose secondary to post-injection adverse reactions, be able to obtain assistance if needed, and should not drive or operate machinery.

If parenteral benzodiazepines are essential for management of post-injection adverse reactions, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Injection site-related adverse events

The most commonly reported injection site-related adverse reaction was pain. The majority of these reactions were reported to be of "mild" to "moderate" severity. In the event of an injection site-related adverse reaction occuring, appropriate measures to manage these events should be taken.

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. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in oral olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). 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. However, the incidence of death was higher in oral olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse reactions (CVAEvents e.g., stroke, transient ischaemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with oral olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All oral olanzapine- and placebo-treated patients who experienced a cerebrovascular event had pre-existing risk factors. Age > 75 years and vascular/mixed type dementia were identified as risk factors for CVAE in association with olanzapine treatment. The efficacy of olanzapine was not established in

these trials.

Parkinson's disease

The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. In clinical trials, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo, and oral olanzapine was not more effective than placebo in the treatment of psychotic symptoms. In these trials, patients were initially required to be stable on the lowest effective dose of anti-Parkinsonian medicinal products (dopamine agonist) and to remain on the same anti-Parkinsonian medicinal products and dosages throughout the study. Oral olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially life-threatening condition associated with antipsychotic medicinal products. Rare cases reported as NMS have also been received in association with oral olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, 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 in accordance with utilised antipsychotic guidelines, e.g., measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter. Patients treated with any antipsychotic medicines, including TOLAZ LA, 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, e.g., at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.

Lipid alterations

Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials. Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic medicines, including TOLAZ LA, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g., at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.

Anticholinergic activity

While olanzapine demonstrated anticholinergic activity in vitro, experience during the clinical trials revealed a low incidence of related events. However, as clinical experience

with 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 oral olanzapine is stopped abruptly.

QT interval

In clinical trials with oral olanzapine, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post-baseline in patients with baseline QTcF<500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. In clinical trials with olanzapine powder for solution for injection or TOLAZ LA, olanzapine was not associated with a persistent increase in absolute QT or in QTc intervals. However, caution should be exercised 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 antagonise 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. In most of these cases, a history of seizures or risk factors for seizures were reported.

Tardive dyskinesia
In comparator studies of one year or less duration, olanzapine was associated with a statistically significant lower incidence of treatment emergent dyskinesia. However, 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
In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine. 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.

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.

Use in elderly (>75 years)
No information on the use of TOLAZ LA in patients > 75 years is available. Due to biochemical and physiological modification and reduction of muscular mass, this formulation is not recommended to be started in this sub-group of patients.

4.5 Drugs interactions
Interaction studies have only been performed in adults.

Caution should be exercised in patients who receive medicinal products that can induce hypotension or sedation.

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. The clinical consequences are likely to be limited, but 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 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. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

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 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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.

New-born 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. Consequently, newborns should be monitored carefully.

Breast-feeding
In a study of oral olanzapine 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

No studies on the effects on the ability to drive and use machines have been performed. As olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

Patients should be advised not to drive or operate machinery for the remainder of the day after each injection due to the possibility of a post-injection syndrome event leading to symptoms consistent with olanzapine overdose.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions seen with olanzapine pamoate

Post-injection syndrome reactions have occurred with TOLAZ LA leading to symptoms consistent with olanzapine overdose. Clinical signs and symptoms included symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsion.

Other adverse reactions observed in patients treated with TOLAZ LA were similar to those seen with oral olanzapine. In clinical trials with TOLAZ LA, the only adverse reaction reported at a statistically significantly higher rate in the TOLAZ LA group than in the placebo group was sedation (TOLAZ LA 8.2%, placebo 2.0%). Among all TOLAZ LA-treated patients, sedation was reported by 4.7% of patients.

In clinical trials with TOLAZ LA, the incidence of injection site-related adverse reactions was approximately 8%. The most commonly reported injection site-related adverse reaction was pain (5%); some other injection site-adverse reactions reported were (in decreasing frequency): nodule-type reactions, erythema-type reactions, non-specific injection-site reactions, irritation, oedema-type reactions, bruising, haemorrhage, and anaesthesia. These events occurred in about 0.1 to 1.1% of patients.

In a review of safety data from clinical trials and spontaneous postmarketing reports, injection site abscess was rarely ($\geq$ 1/10,000 to < 1/1,000) reported.

Adverse reactions seen with olanzapine

The undesirable effects listed below have been observed following administration of

olanzapine.

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 and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the data available).

Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and the lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia [11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria Increased appetite	Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases[11]	Hypothermia[12]	
Nervous system disorders				
Somnolence	Dizziness Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported[11] Dystonia (including oculogyration)[11]	Neuroleptic malignant syndrome[12] Discontinuation symptoms[7, 12]	

		Tardive dyskinesia[11] Amnesia [9] Dysarthria Stuttering[11] Restless Legs Syndrome[11]		
Cardiac disorders				
		Bradycardia QTc prolongation	Ventricular tachycardia / fibrillation, sudden death [11]	
Vascular disorders				
Orthostatic hypotension[10]		Thromboembolism (including pulmonary embolism and deep vein thrombosis)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment		Hepatitis (including hepatocellular, cholestatic or mixed liver injury) [11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	

Renal and urinary disorders				
		Urinary incontinence, Urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia / breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				
	Asthenia Fatigue Oedema Pyrexia[10] Injection site pain		Injection site abscess	
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase [10] High uric acid [10]	Increased total bilirubin		

[1] Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Following short-term treatment (median duration 47 days), weight gain ≥ 7% of baseline body weight was very common (22.2%), ≥ 15% was common (4.2%) and ≥ 25% was uncommon (0.8%). Patients gaining ≥ 7%, ≥ 15% and ≥ 25% of their baseline body weight with long-term exposure (at least 48 weeks) were very common (64.4%, 31.7% and 12.3% respectively).

[2] Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline.

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

[6] In clinical trials, the incidence of Parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of Parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

[7] Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea and vomiting have been reported when olanzapine is stopped abruptly.

[8] In clinical trials of up to 12 weeks, plasma prolactin concentrations exceeded the upper limit of normal range in approximately 30% of olanzapine-treated patients with normal baseline prolactin value. In the majority of these patients the elevations were generally mild, and remained below two times the upper limit of normal range.

[9] Adverse event identified from clinical trials in the Olanzapine Integrated Database.

[10] As assessed by measured values from clinical trials in the Olanzapine Integrated Database.

[11] Adverse event identified from spontaneous post-marketing reporting with frequency determined utilising the Olanzapine Integrated Database.

[12] Adverse event identified from spontaneous post-marketing reporting with frequency estimated at the upper limit of the 95% confidence interval utilising the Olanzapine Integrated Database.

Long-term exposure (at least 48 weeks)

The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations

In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo. 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.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. 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 ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥ 7% from baseline body weight in 39.9% of patients.

Paediatric population

Olanzapine is not indicated for the treatment of children and adolescent patients below 18 years. Although no clinical studies designed to compare adolescents to adults have been conducted, data from the adolescent trials were compared to those of the adult trials.

The following table summarises the adverse reactions reported with a greater frequency in adolescent patients (aged 13-17 years) than in adult patients or adverse reactions only identified during short-term clinical trials in adolescent patients. Clinically significant weight gain (≥ 7%) appears to occur more frequently in the adolescent population compared to adults with comparable exposures. The magnitude of weight gain and the proportion of adolescent patients who had clinically significant weight gain were greater with long-term exposure (at least 24 weeks) than with short-term exposure.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10).

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite *Common:* Elevated cholesterol levels[15]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence)
Gastrointestinal disorders *Common:* Dry mouth
Hepatobiliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST)
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16]

[13] Following short-term treatment (median duration 22 days), weight gain ≥ 7% of baseline body weight (kg) was very common (40.6%), ≥ 15% of baseline body weight was common (7.1%) and ≥ 25% was common (2.5%). With long-term exposure (at least 24 weeks), 89.4% gained ≥ 7%, 55.3% gained ≥ 15% and 29.1% gained ≥ 25% of their baseline body weight.

[14] Observed for fasting normal levels at baseline (< 1.016 mmol/l) which increased to high (≥ 1.467 mmol/l) and changes in fasting triglycerides from borderline at baseline (≥ 1.016 mmol/l - < 1.467 mmol/l) to high (≥ 1.467 mmol/l).

[15] Changes in total fasting cholesterol levels from normal at baseline (< 4.39 mmol/l) to high (≥ 5.17 mmol/l) were observed commonly. Changes in total fasting cholesterol levels from borderline at baseline (≥ 4.39 - < 5.17 mmol/l) to high (≥ 5.17 mmol/l) were very common.

[16] Elevated plasma prolactin levels were reported in 47.4% of adolescent patients.

4.9 Overdose

While overdose is less likely with parenteral than oral medicinal products, reference information for oral olanzapine overdose is presented below:

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 oral overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management

There is no specific antidote for olanzapine. 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 Mechanism of Action

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

5.2 Pharmacodynamic properties

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

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

In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki < 100 nM) for serotonin 5-HT2A/2C, 5-HT3, 5-HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors M1-M5; α-1 adrenergic; and histamine H1 receptors. Animal

behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater in vitro affinity for serotonin 5-HT2 than dopamine D2 receptors and greater 5-HT2 than D2 activity in in vivo models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. 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.

In a Positron Emission Tomography (PET) study in patients treated with TOLAZ LA (300 mg/4 weeks), mean D2 receptor occupancy was 60% or higher at the end of a 6-month period, a level consistent with that found during treatment with oral olanzapine.

Clinical efficacy

The effectiveness of TOLAZ LA in the treatment and maintenance treatment of schizophrenia is consistent with the established effectiveness of the oral formulation of olanzapine.

A total of 1469 patients with schizophrenia were included in 2 pivotal trials:

The first, an 8-week, placebo-controlled trial conducted in adult patients (n=404) who were experiencing acute psychotic symptoms. Patients were randomised to receive injections of TOLAZ LA 405 mg every 4 weeks, 300 mg every 2 weeks, 210 mg every 2 weeks, or placebo every 2 weeks. No oral antipsychotic supplementation was allowed. Total Positive and Negative Symptom Scores (PANSS) showed significant improvement from baseline (baseline mean Total PANSS Score 101) to endpoint (mean changes -22.57, -26.32, -22.49 respectively) with each dose of TOLAZ LA (405 mg every 4 weeks, 300 mg every 2 weeks, and 210 mg every 2 weeks) as compared to placebo (mean change -8.51). Visitwise mean change from baseline to endpoint in PANSS Total Score indicated that by Day 3, patients in the 300 mg/2 weeks and 405 mg/4 weeks treatment groups had statistically significantly greater reductions in PANSS Total Score compared to placebo (-8.6, -8.2, and -5.2, respectively). All 3 TOLAZ LA treatment groups showed statistically significantly greater improvement than placebo beginning by end of Week 1. These results support efficacy for TOLAZ LA over 8 weeks of treatment and a drug effect that was observed as early as 1 week after starting treatment with TOLAZ LA.

The second, a long-term study in clinically stable patients (n=1065) (baseline mean Total PANSS Score 54.33 to 57.75), who were initially treated with oral olanzapine for 4 to 8 weeks and then switched to continue on oral olanzapine or to TOLAZ LA for 24 weeks. No oral antipsychotic supplementation was allowed. TOLAZ LA treatment groups of 150 mg and 300 mg given every 2 weeks (doses pooled for analysis) and 405 mg given every 4 weeks were non-inferior to the combined doses of 10, 15 and 20 mg of oral olanzapine (doses pooled for analysis) as measured by rates of exacerbation of symptoms of schizophrenia (respective exacerbation rates, 10%, 10%, 7%). Exacerbation was measured by worsening of items on the PANSS derived BPRS Positive Scale and hospitalisation due to worsening of positive psychotic symptoms. The combined 150 mg and 300 mg/2 week treatment group was non-

inferior to the 405 mg/4 week treatment group (exacerbation rates 10% for each group) at 24 weeks after randomisation.

Paediatric population

TOLAZ LA has not been studied in the paediatric population. Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term oral olanzapine studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Oral olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with oral 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. There are no controlled data on maintenance of effect or long term safety. Information on long term safety is primarily limited to open-label, uncontrolled data.

5.3 Pharmacokinetic properties

Absorption

Olanzapine is metabolised in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites; both exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent, olanzapine.

After a single IM injection with TOLAZ LA, the slow dissolution of the olanzapine pamoate salt in muscle tissue begins immediately and provides a slow continuous release of olanzapine for more than four weeks. The release becomes diminishingly smaller within eight to twelve weeks. Antipsychotic supplementation is not required at the initiation of TOLAZ LA treatment.

The combination of the release profile and the dosage regimen (IM injection every two or four weeks) result in sustained olanzapine plasma concentrations. Plasma concentrations remain measurable for several months after each TOLAZ LA injection. The half-life of olanzapine after TOLAZ LA is 30 days compared to 30 hours following oral administration. The absorption and elimination are complete approximately six to eight months after the last injection.

Distribution

Oral olanzapine is rapidly distributed. The plasma protein binding of olanzapine is about 93% over the concentration range of 7 to about 1000 ng/mL. In plasma, olanzapine is bound to albumin and α1-acid glycoprotein.

After repeated IM injections with 150 to 300 mg TOLAZ LA every two weeks, the 10th to 90th percentile of steady-state plasma concentrations of olanzapine were between 4.2 and 73.2 ng/ml. The plasma concentrations of olanzapine observed across the dose range of 150mg every 4 weeks to 300mg every 2 weeks illustrate increased systemic olanzapine exposure with increased TOLAZ LA doses. During the initial three months of treatment with TOLAZ LA, accumulation of olanzapine was observed but there was

no additional accumulation during long-term use (12 months) in patients who were injected with up to 300 mg every two weeks.

Elimination

Olanzapine plasma clearance after oral olanzapine is lower in females (18.9 l/hr) versus males (27.3 l/hr), and in non-smokers (18.6 l/hr) versus smokers (27.7 l/hr). Similar pharmacokinetic differences between males and females and smokers and non-smokers were observed in TOLAZ LA clinical trials. However, the magnitude of the impact of gender, or smoking on olanzapine clearance is small in comparison to the overall variability between individuals.

Elderly

No specific investigations have been conducted in the elderly with TOLAZ LA. TOLAZ LA is not recommended for treatment in the elderly population (65 years and over) unless a well-tolerated and effective dosage regimen using oral olanzapine has been established. In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hours) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia >65 years of age, dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

Renal impairment

In renally impaired patients (creatinine clearance < 10 ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hours) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites. Although patients with renal impairment were not studied with TOLAZ LA, it is recommended that a well-tolerated and effective dosage regimen using oral olanzapine is established in patients with renal impairment before treatment with TOLAZ LA is initiated.

Hepatic impairment

A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the pharmacokinetics of orally administered olanzapine (2.5 - 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-time compared to subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).

Although patients with hepatic impairment were not studied with TOLAZ LA, it is recommended that a well-tolerated and effective dosage regimen using oral olanzapine is established in patients with hepatic impairment before treatment with TOLAZ LA is initiated.

In a study of oral olanzapine given to Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Preclinical safety studies were performed using olanzapine pamoate monohydrate. The main findings found in repeat-dose toxicity studies (rat, dog), in a 2-year rat carcinogenicity study, and in toxicity to reproduction studies (rat, rabbit) were limited to injection-site reactions for which no NOAEL could be determined. No new toxic effect resulting from systemic exposure to olanzapine could be identified. However, systemic concentrations in these studies were generally less than that seen at effect levels in the oral studies; thus the information on oral olanzapine is provided below for reference.

Acute (single-dose) toxicity

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

Repeated-dose toxicity

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

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

Reproductive toxicity

Olanzapine had no teratogenic effects. Sedation affected mating performance of male rats. Oestrous cycles were affected at doses of 1.1 mg/kg (3-times the maximum human dose) and reproduction parameters were influenced in rats given 3 mg/kg (9-times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal

development and transient decreases in offspring activity levels were seen.

Mutagenicity

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

Carcinogenicity

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

7 Description

Tolaz LA 210mg :
Each combipack contains :
A. Vial containing yellow crystalline Olanzapine pamoate monohydrate powder,
B. Vial of vehicle containing clear colorless to slight yellow mobile solution,
C. One 3-ml syringe,
D. Three 19 gauge, 1.5 inch (38mm) Hypodermic Needles with protection device.

Tolaz LA 300mg :
Each combipack contains :
A. Vial containing yellow crystalline Olanzapine pamoate monohydrate powder,
B. Vial of vehicle containing clear colorless to slight yellow mobile solution,
C. One 3-ml syringe,
D. Three 19 gauge, 1.5 inch (38mm) Hypodermic Needles with protection device.

Tolaz LA 405mg :
Each combipack contains :
A. Vial containing yellow crystalline Olanzapine pamoate monohydrate powder,
B. Vial of vehicle containing clear colorless to slight yellow mobile solution,
C. One 3-ml syringe,
D. Three 19 gauge, 1.5 inch (38mm) Hypodermic Needles with protection device.

8 Pharmaceutical particulars

8.1 Incompatibilities

This medicinal product must not be mixed with other medicinal products

8.2 Shelf-life

Do not use later than date of Expiry

8.3 Packaging information

Available in combi pack

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C, protected from light and moisture.
DO NOT REFRIGERATE OR FREEZE.
Keep out of reach of children.

9 Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet

What is in this leaflet

9.1 What TOLAZ LA is and what it is used for

TOLAZ LA contains the active substance olanzapine. TOLAZ LA belongs to a group of medicines called antipsychotics and is used to treat schizophrenia - a disease with symptoms such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, and becoming withdrawn. People with this disease may also feel depressed, anxious or tense.

TOLAZ LA is intended for adult patients who are sufficiently stabilised during treatment with oral olanzapine.

9.2 . What you need to know before you are given TOLAZ LA

You should not be given TOLAZ LA if you have:

- an allergy (hypersensitivity) to olanzapine or any of the other ingredients of this medicine. **An allergic reaction** may be recognised as a rash, itching, a swollen face, swollen lips or shortness of breath. If this has happened to you, tell your nurse or doctor.
- been previously diagnosed with eye problems such as certain kinds of glaucoma (increased pressure in the eye).

Warnings and precautions

Talk to your doctor or nurse before you are given TOLAZ LA

- ***An uncommon but serious reaction might occur after you receive each injection.*** TOLAZ LA can sometimes enter the bloodstream too quickly. If this happens, you may have the symptoms listed below after your injection. In some cases, these symptoms can lead to unconsciousness.
- excessive sleepiness
- dizziness
- confusion
- disorientation
- irritability
- anxiety

- aggression
- increase in blood pressure
- difficulty talking
- weakness
- difficulty walking
- muscle stiffness or shaking
- convulsions

These symptoms typically resolve within 24 to 72 hours after your injection. After each injection you will be observed in your healthcare facility for at least 3 hours for the symptoms listed above.

Although unlikely, you may get the symptoms more than 3 hours after the injection. If this happens, contact your doctor or nurse immediately. Because of this risk, do not drive or operate machinery for the remainder of the day after each injection.

- Tell the doctor or nurse if you feel dizzy or faint after the injection. You will probably need to lie down until you feel better. The doctor or nurse may also want to measure your blood pressure and pulse.
- The use of TOLAZ LA in elderly patients with dementia (confusion and memory loss) is not recommended as it may have serious side effects.
- Very rarely, medicines of this type may cause unusual movements mainly of the face or tongue or a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness. If this happens after you have been given TOLAZ LA, tell your doctor or nurse immediately.
- Weight gain has been seen in patients taking TOLAZ LA. You and your doctor should check your weight regularly. Consider referral to a dietician or help with a diet plan if necessary.
- High blood sugar and high levels of fat (triglycerides and cholesterol) have been seen in patients taking TOLAZ LA. Your doctor should do blood tests to check blood sugar and certain fat levels before you start taking TOLAZ LA and regularly during treatment. Tell the doctor if you or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.

Tell your doctor as soon as possible if any of the following applies to you:
• Stroke or “mini” stroke (temporary symptoms of stroke)
• Parkinson’s disease
• Prostate problems
• A blocked intestine (Paralytic ileus)
• Liver or kidney disease
• Blood disorders
• A recent heart attack, heart disease, sick sinus syndrome, (abnormal heart rhythms), unstable angina or low blood pressure
• Diabetes
• Seizures
• If you know that you may have salt depletion as a result of prolonged severe diarrhoea and vomiting (being sick) or usage of diuretics (water tablets)

As a routine precaution, if you are over 65 years your doctor may monitor your blood pressure.

TOLAZ LA is not recommended to be started if you are over 75 years.

Children and adolescents
TOLAZ LA is not for patients who are under 18 years.

Other medicines and TOLAZ LA
Tell your doctor if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor if you are taking:
- medicines for Parkinson's disease.

- carbamazepine (an anti-epileptic and mood stabiliser), fluvoxamine (an antidepressant) or ciprofloxacin (an antibiotic) - it may be necessary to change your TOLAZ LA dose.

If you are already taking antidepressants, medicines for anxiety or to help you sleep (tranquillisers), you may feel drowsy if TOLAZ LA is given.

TOLAZ LA with alcohol
Do not drink any alcohol if you have been given TOLAZ LA as together with alcohol it may make you feel drowsy.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this injection.
You should not be given this injection if you are breast-feeding as small amounts of olanzapine can pass into breast milk.

The following symptoms may occur in newborn babies, of mothers that have used ZYPAHDERA in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Driving and using machines
Do not drive or operate machinery for the remainder of the day after each injection.

9.3 How TOLAZ LA is given
Your doctor will decide how much TOLAZ LA you need and how often you need to be given an injection. TOLAZ LA is given in doses of 150 mg to 300 mg every 2 weeks or 300 mg to 405 mg every 4 weeks.
TOLAZ LA comes as a powder which your doctor or nurse will make into a suspension that will then be injected into the muscle in your buttock.

If you are given more TOLAZ LA than needed
This medicine will be given to you under medical supervision, it is therefore unlikely that you will be given too much.
Patients who have been given too much olanzapine have also experienced the following symptoms:

• rapid beating of the heart, agitation/aggressiveness, problems with speech, unusual movements (especially of the face or tongue) and reduced level of consciousness.
Other symptoms may include:
• acute confusion, seizures (epilepsy), coma, a combination of fever, faster breathing, sweating, muscle stiffness, and drowsiness or sleepiness; slower breathing, aspiration, high or low blood pressure, abnormal rhythms of the heart.

Contact your doctor or hospital straight away if you experience any of the above symptoms.

If you miss an injection of TOLAZ LA
Do not stop your treatment just because you feel better. It is important that you carry on receiving TOLAZ LA for as long as your doctor has told you to.

If you miss an injection, you should contact your doctor to arrange your next injection as soon as you can

If you have any further questions on the use of this medicine, ask your doctor or nurse.

9.4 Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you have:
- excessive sleepiness, dizziness, confusion, disorientation, difficulty talking, difficulty walking, muscle stiffness or shaking, weakness, irritability, aggression, anxiety, increase in blood pressure, or convulsions and can lead to unconsciousness. These signs and symptoms can sometimes occur as a result of TOLAZ LA entering the bloodstream too quickly (a common side effect that may affect up to1 in10 people);
- unusual movement (a common side effect that may affect up to 1 in 10 people) mainly of the face or tongue;
- blood clots in the veins (an uncommon side effect that may affect up to 1in 100 people) especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately;
- a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness (the frequency of this side effect cannot be estimated from the available data).

Other common side effects (may affect up to 1 in 10 people) with TOLAZ LA include sleepiness and injection site pain.

Rare side effects (may affect up to 1 in 1000 people) with TOLAZ LA include injection site infection.
The side effects listed below have been observed when oral olanzapine has been given but may occur following administration of TOLAZ LA.

Other very common side effects (may affect more than 1 in 10 people) include weight gain; and increases in levels of prolactin in the blood. In the early stages of treatment, some people may feel dizzy or faint (with a slow heart rate), especially when getting up from a lying or sitting position. This will usually pass on its own but if it does not, tell your doctor.

Other common side effects (may affect up to 1 in 10 people) include changes in the levels of some blood cells, circulating fats and in early treatment, temporary increases in liver enzymes; increases in the level of sugars in the blood and urine; increases in levels of uric acid and creatine phosphokinase in the blood; feeling more hungry; dizziness; restlessness; tremor; unusual movements (dyskinesias); constipation; dry mouth; rash; loss of strength; extreme tiredness; water retention leading to swelling of the hands, ankles or feet; fever; joint pain; and sexual dysfunctions such as decreased libido in males and females or erectile dysfunction in males.

Other uncommon side effects (may affect up to 1 in 100 people) include hypersensitivity (e.g. swelling in the mouth and throat, itching; rash); diabetes or the worsening of diabetes, occasionally associated with ketoacidosis (ketones in the blood and urine) or coma; seizures, usually associated with a history of seizures (epilepsy); muscle stiffness or spasms (including eye movements); restless legs syndrome; problems with speech; stuttering; slow heart rate; sensitivity to sunlight; bleeding from the nose: abdominal distension; memory loss or forgetfulness; urinary incontinence; lack of ability to urinate; hair loss; absence or decrease in menstrual periods; and changes in breasts in males and females such as an abnormal production of breast milk or abnormal growth.

Rare side effects (may affect up to 1 in 1000 people) include lowering of normal body temperature; abnormal rhythms of the heart; sudden unexplained death; inflammation of the pancreas causing severe stomach pain, fever and sickness; liver disease appearing as yellowing of the skin and white parts of the eyes; muscle disease presenting as unexplained aches and pains; and prolonged and/or painful erection.

Very rare side effects include serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as 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).

While taking olanzapine, elderly patients with dementia may suffer from stroke, pneumonia, urinary incontinence, falls, extreme tiredness, visual hallucinations, a rise in body temperature, redness of the skin and have trouble walking. Some fatal cases have been reported in this particular group of patients.

In patients with Parkinson's disease oral olanzapine may worsen the symptoms

9.5 How to store TOLAZ LA

Store at a temperature not exceeding 30°C, protected from light and moisture.
DO NOT REFRIGERATE OR FREEZE.
Use within 24 hours after reconstitution.
Discard the vials, syringe, needle and any unused vehicle.

Keep this medicine out of the sight and reach of children.
The injection must not be given after the expiry date which is stated on the carton.

Once withdrawn from vial into syringe suspension should be used immediately

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

9.6 Contents of the pack and other information

Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection 210mg
TOLAZ LA 210 mg/Vial
Each Combipack Contains:
A. Vial of Olanzapine Pamoate Prolonged Release Powder for Suspension
Each Vial contains:
Olanzapine embonate Monohydrate Ph.Eur
(Olanzapine Pamoate Monohydrate) equivalent to Olanzapine 210 mg
After reconstitution each ml of suspension contains 150mg Olanzapine.
B. Vial of Vehicle 3 ml
Clear, colorless to slight yellow solution contains:

Mannitol I.P.	5.070% w/v
Sodium Carboxymethyl Cellulose I.P.	0.770% w/v
Polysorbate 80 I.P.	0.025% w/v
Hydrochloric acid I.P.	q.s.
Sodium Hydroxide I.P.	q.s.
Water for Injection I.P.	q.s. to 100%

C. One 3ml Disposable Syringe
D. Three 19 gauge, 1.5 inch (38mm) Hypodermic Needles with protection device.

Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection 300mg
TOLAZ LA 300 mg/Vial
Each Combipack Contains:
A. Vial of Olanzapine Pamoate Prolonged Release Powder for Suspension
Each Vial contains:
Olanzapine embonate Monohydrate Ph.Eur
(Olanzapine Pamoate Monohydrate) equivalent to Olanzapine 300 mg
After reconstitution each ml of suspension contains 150mg Olanzapine.
B. Vial of Vehicle 3 ml
Clear, colorless to slight yellow solution contains:

Mannitol I.P.	5.070% w/v
Sodium Carboxymethyl Cellulose I.P.	0.770% w/v
Polysorbate 80 I.P.	0.025% w/v
Hydrochloric acid I.P.	q.s.
Sodium Hydroxide I.P.	q.s.
Water for Injection I.P.	q.s. to 100%

C. One 3ml Disposable Syringe
D. Three 19 gauge, 1.5 inch (38mm) Hypodermic Needles with protection device.

Olanzapine Pamoate Prolonged Release Powder for Suspension for IM Injection 405mg
TOLAZ LA 405 mg/Vial
Each Combipack Contains:
A. Vial of Olanzapine Pamoate Prolonged Release Powder for Suspension
Each Vial contains:
Olanzapine embonate Monohydrate Ph.Eur
(Olanzapine Pamoate Monohydrate) equivalent to Olanzapine 405 mg

After reconstitution each ml of suspension contains 150mg Olanzapine.
B. Vial of Vehicle 3 ml
Clear, colorless to slight yellow solution contains:

Mannitol I.P.	5.070% w/v
Sodium Carboxymethyl Cellulose I.P.	0.770% w/v
Polysorbate 80 I.P.	0.025% w/v
Hydrochloric acid I.P.	q.s.
Sodium Hydroxide I.P.	q.s.
Water for Injection I.P.	q.s. to 100%

C. One 3ml Disposable Syringe
D. Three 19 gauge, 1.5 inch (38mm) Hypodermic Needles with protection device.

Qualitative and quantitative formula:
Pamoic acid
Dimethyl sulfoxide
Acetone
Mannitol
Sodium Carboxymethyl Cellulose
Polysorbate 80
Hydrochloric acid
Sodium Hydroxide

10 Details of manufacturer
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist . Mehsana India
At : Rampurghat Road, Paonta Sahib, Dist. Sirmour-173 025 (H.P.)

11 Details of permission or licence number with date
Kit pack mfg lic no. NL-MB/2014-135 dated 15.10.2020

12. Date of revision
Nov 2020

MARKETED BY
TORRENT PHARMACEUTICALS LTD.
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IN/ TOLAZ LA/NOV-20/04/PI