# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Ceyxa 10 mg powder for solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg olanzapine. After reconstitution each ml of the solution contains 5 mg olanzapine.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for solution for injection
Yellow lyophilised powder in a clear glass vial.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adults*
Ceyxa powder for solution for injection is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or manic episode, when oral therapy is not appropriate. Treatment with Ceyxa powder for solution for injection should be discontinued and the use of oral olanzapine should be initiated as soon as clinically appropriate.

## 4.2 Posology and method of administration

*Adults*
For intramuscular use. Do not administer intravenously or subcutaneously. Ceyxa powder for solution for injection is intended for short term use only, for up to a maximum of three consecutive days.

The maximum daily dose of olanzapine (including all formulations of olanzapine) is 20 mg.

The recommended initial dose for olanzapine injection is 10 mg, administered as a single intramuscular injection. A lower dose (5 mg or 7.5 mg) may be given, on the basis of individual clinical status, which should also include consideration of medicinal products already administered either for maintenance or acute treatment (see section 4.4). A second injection, 5-10 mg, may be administered 2 hours after the first injection on the basis of individual clinical status.
Not more than three injections should be given in any 24-hour period and the maximum daily dose of olanzapine of 20 mg (including all formulations) should not be exceeded.

Ceyxa powder for solution for injection should be reconstituted in accordance with the recommendation in section 6.6.

For further information on continued treatment with oral olanzapine (5 to 20 mg daily), refer to the Summary of Product Characteristics for the relevant product Olanzapine film-coated tablets or Olanzapine orodispersible tablets.

Special populations

*Elderly*
The recommended starting dose in elderly patients (> 60 years) is 2.5 - 5 mg. Depending on the patient's clinical status (see section 4.4), a second injection, 2.5 - 5 mg, may be administered 2 hours after the first injection. Not more than 3 injections should be given in any 24-hour period and the maximum daily dose of 20 mg (including all formulations) of olanzapine should not be exceeded.

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

*Smokers*
The dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by

smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

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

(See sections 4.5 and 5.2.)

*Paediatric population*
There is no experience in children. Ceyxa powder for solution for injection is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

The efficacy of IM olanzapine has not been established in patients with agitation and disturbed behaviours related to conditions other than schizophrenia or manic episode.

Unstable medical conditions
IM olanzapine should not be administered to patients with unstable medical conditions, such as acute myocardial infarction, unstable angina pectoris, severe hypotension and/or bradycardia, sick sinus syndrome, or following heart surgery. If the patient's medical history with regard to these unstable medical conditions cannot be determined, the risks and benefits of IM olanzapine should be considered in relation to other alternative treatments.

Concomitant use of benzodiazepines and other medicinal products
Special caution is necessary in patients who have received treatment with other medicinal products having haemodynamic properties similar to those of intramuscular olanzapine including other antipsychotics (oral and/or intramuscular) and benzodiazepines (see section 4.5). Temporal association of treatment with IM olanzapine with hypotension, bradycardia, respiratory depression and death has been very rarely (< 0.01%) reported particularly in

patients who have received benzodiazepines and/or other antipsychotics (see section 4.8).

Simultaneous injection of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation, cardiorespiratory depression and in very rare cases, death (see sections 4.5 and 6.2). If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least one hour after IM olanzapine administration. If the patient has received parenteral benzodiazepine, IM olanzapine administration should only be considered after careful evaluation of clinical status and the patient should be closely monitored for excessive sedation and cardiorespiratory depression.

Hypotension

It is extremely important that patients receiving intramuscular olanzapine should be closely observed for hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation, particularly for the first 4 hours following injection and close observation should be continued after this period if clinically indicated. Blood pressure, pulse, respiratory rate and level of consciousness should be observed regularly and remedial treatment provided if required. Patients should remain recumbent if dizzy or drowsy after injection until examination indicates that they are not experiencing hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation.

The safety and efficacy of IM olanzapine has not been evaluated in patients with alcohol or drug intoxication (either with prescribed or illicit drugs) (see section 4.5).

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 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 olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient ischemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All 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 (see section 4.8), and 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. 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 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 (see section 4.8). 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 olanzapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly, 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 (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic medicines, including

olanzapine, 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 oral 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 (see section 4.8).

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

QT interval
In clinical trials with oral administration, 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, 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 oral 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 oral olanzapine clinical trials. It is recommended that blood pressure is measured periodically in patients over 65 years.

Sudden cardiac death:

In post marketing 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.

## 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

IM olanzapine has not been studied in patients with alcohol or drug intoxication (see section 4.4).

Caution should be exercised in patients who consume alcohol or receive medicinal products that can induce hypotension, bradycardia, respiratory or central nervous system depression (see section 4.4).

Potential for interaction following intramuscular injection
In a single dose intramuscular study of olanzapine 5 mg, administered 1 hour before intramuscular lorazepam 2 mg (metabolised by glucuronidation), the pharmacokinetics of both medicines were unchanged. However, the combination added to the somnolence observed with either medicine alone. Concomitant injection of olanzapine and parenteral benzodiazepine is not recommended (see sections 4.4 and 6.2).

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 (see section 4.2).

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

Decreased bioavailability
Activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60% and should be taken at least 2 hours before or after olanzapine.

Fluoxetine (a CYP2D6 inhibitor), single doses of antacid (aluminium, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.

Potential for olanzapine to affect other medicinal products

Olanzapine may antagonise the effects of direct and indirect dopamine agonists. (see section 6.2).

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.

The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended (see section 4.4).

QTc interval
Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

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

New born infant 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 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 (see section 5.3 for preclinical information).

## 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. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

## 4.8 Undesirable effects

Summary of the safety profile
A common (≥ 1/100 to < 1/10) undesirable effect associated with the use of intramuscular olanzapine in clinical trials was somnolence.

In post marketing reports, temporal association of treatment with IM olanzapine with cases of respiratory depression, hypotension or bradycardia and death have been very rarely reported, mostly in patients who concomitantly received benzodiazepines, and/or other antipsychotic medicinal products or who were treated in excess of olanzapine recommended daily doses (see sections 4.4 and 4.5).

The following table is based on the undesirable effects and laboratory investigations from clinical trials with olanzapine powder for solution for injection rather than oral olanzapine.

| |
|---|
| **Cardiac disorders**<br>*Common (≥1/100 to <1/10):* Bradycardia with or without hypotension or syncope, tachycardia.<br>*Uncommon (≥1/1,000 to <1/100):* Sinus pause. |
| **Vascular Disorders**<br>*Common (≥1/100 to <1/10):* Postural hypotension, hypotension. |
| **Respiratory , thoracic and mediastinal disorders**<br>*Uncommon (≥1/1,000 to <1/100):* Hypoventilation. |
| **General disorders and administration site conditions**<br>*Common (≥1/100 to <1/10):* Injection site discomfort. |

The undesirable effects listed below have been observed following administration of oral and prolonged release intramuscular injection olanzapine, but may also occur following administration of Ceyxa 10 mg powder for solution for injection.

*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 (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases (see section 4.4), 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 available data).

| **Very common** | **Common** | **Uncommon** | **Rare** | **Not known** |
|---|---|---|---|---|
| **Blood and lymphatic system disorders** | | | | |
| | Eosinophilia<br>Leukopenia[10]<br>Neutropenia[10] | | Thrombocytopenia[11] | |
| **Immune system disorders** | | | | |
| | | Hypersensitivity[11] | | |
| **Metabolism and nutrition disorders** | | | | |
| Weight gain[1] | Elevated cholesterol levels[2,3]<br>Elevated glucose levels[4]<br>Elevated triglyceride levels[2,5]<br>Glucosuria<br>Increased appetite | Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4)[11] | Hypothermia[12] | |

| | | | | |
|---|---|---|---|---|
| **Nervous system disorders** | | | | |
| Somnolence | Dizziness<br>Akathisia[6]<br>Parkinsonism[6]<br>Dyskinesia[6] | Seizures where in most cases a history of seizures or risk factors for seizures were reported[11]<br>Dystonia (including oculogyration)[11]<br>Tardive dyskinesia[11]<br>Amnesia[9]<br>Dysarthria<br>Stuttering[11,13]<br>Restless Legs Syndrome[11] | Neuroleptic malignant syndrome (see section 4.4)[12]<br>Discontinuation symptoms[7,12] | |
| **Cardiac disorders** | | | | |
| | | Bradycardia<br>QTc prolongation (see section 4.4) | Ventricular tachycardia/fibrillation, sudden death (see section 4.4)[11] | |
| **Vascular disorders** | | | | |
| Orthostatic hypotension[10] | | Thromboembolism (including pulmonary embolism and deep vein thrombosis) (see section4.4) | | |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| | | Epistaxis[9] | | |
| **Gastrointestinal disorders** | | | | |
| | Mild, transient anticholinergic effects including constipation and dry mouth | Abdominal distension[9]<br>Salivary hypersecretion[11] | Pancreatitis[11] | |
| **Hepatobiliary disorders** | | | | |
| | Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4) | | Hepatitis (including hepatocellular, cholestatic or mixed liver injury)[11] | |
| **Skin and subcutaneous tissue disorders** | | | | |
| | Rash | Photosensitivity reaction<br>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 (see section 4.6) |
| **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] | | | |
| **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.

[13]Undesirable effects listed and observed following administration of oral and LAIM olanzapine, which may also occur following administration of RAIM olanzapine.

*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 (see section 4.4). 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

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

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

*Management of overdose*
There is no specific antidote for olanzapine.

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

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

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

Pharmacodynamic effects
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-$HT_{2A/2C}$, 5-$HT_3$, 5-$HT_6$; dopamine $D_1$, $D_2$, $D_3$, $D_4$, $D_5$; cholinergic muscarinic receptors $m_1$-$m_5$; a-1 adrenergic; and histamine $H_1$ 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-$HT_2$ than dopamine $D_2$ receptors and greater 5-$HT_2$ than $D_2$ activity *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 single oral dose (10 mg) Positron Emission tomography (PET) study in healthy volunteers, olanzapine produced a higher 5-$HT_{2A}$ than dopamine D2 receptor occupancy. In addition, a Single Photon Emission Computed Tomography (SPECT) imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal $D_2$ occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

Clinical efficacy

In two of two placebo and two of three comparator controlled trials with oral olanzapine in over 2,900 schizophrenic patients presenting with both positive and negative symptoms, olanzapine was associated with statistically significantly greater improvements in negative as well as positive symptoms.

In a multinational, double-blind, comparative study of schizophrenia, schizoaffective, and related disorders which included 1,481 patients with varying degrees of associated depressive symptoms (baseline mean of 16.6 on the Montgomery-Asberg Depression Rating Scale), a prospective secondary analysis of baseline to endpoint mood score change demonstrated a statistically significant improvement (p=0.001) favouring oral olanzapine (-6.0) versus haloperidol (-3.1).

In patients with manic or mixed episode of bipolar disorder, oral olanzapine demonstrated superior efficacy to placebo and valproate semisodium (divalproex) in reduction of manic symptoms over 3 weeks. Oral olanzapine also demonstrated comparable efficacy results to haloperidol in terms of the proportion of patients in symptomatic remission from mania and depression at 6 and 12 weeks. In a co-therapy study of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of oral olanzapine 10 mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

In a 12-month recurrence prevention study in manic episode patients who achieved remission on olanzapine and were then randomised to olanzapine or placebo, olanzapine demonstrated statistically significant superiority over placebo on the primary endpoint of bipolar recurrence. Olanzapine also showed a statistically significant advantage over placebo in terms of preventing either recurrence into mania or recurrence into depression.

In a second 12-month recurrence prevention study in manic episode patients who achieved remission with a combination of olanzapine and lithium and were then randomised to olanzapine or lithium alone, olanzapine was statistically non-inferior to lithium on the primary endpoint of bipolar recurrence (olanzapine 30.0%, lithium 38.3%; p = 0.055).

In an 18-month co-therapy study in manic or mixed episode patients stabilised with olanzapine plus a mood stabiliser (lithium or valproate), long-term olanzapine co-therapy with lithium or valproate was not statistically significantly superior to lithium or valproate alone in delaying bipolar recurrence, defined according to syndromic (diagnostic) criteria.

## 5.2 Pharmacokinetic properties

In a pharmacokinetic study in healthy volunteers, a dose of 5 mg of Olanzapine powder for solution for injection produced a maximum plasma concentration (Cmax) approximately 5 times higher than that seen with the same dose of olanzapine administered orally. The Cmax occurs earlier after intramuscular compared to oral use (15 to 45 minutes versus 5 to 8 hours). As with oral use, Cmax and area under the curve after intramuscular use are directly proportional to the dose administered. For the same dose of olanzapine administered intramuscularly and orally, the associated area under the curve, half-life, clearance and volume of distribution are similar. The metabolic profiles following intramuscular and oral use are similar.

In non-smoking versus smoking subjects (males and females) administered olanzapine intramuscularly the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr).

Additional pharmacokinetic data following administration of oral olanzapine are described below.

Distribution
The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1,000 ng/ml. Olanzapine is bound predominantly to albumin and α1-acid-glycoprotein.

Biotransformation
Olanzapine is metabolised in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and 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.

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

In healthy elderly (65 and over) versus non-elderly subjects administered oral olanzapine, the mean elimination half-life was prolonged (51.8 versus 33.8 hr) 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 nonelderly. 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.

In female versus male subjects administered oral olanzapine the mean elimination half life was somewhat prolonged (36.7 versus 32.3 hrs) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20 mg) demonstrated a comparable safety profile in female (n=467) as in male patients (n=869).

Renal impairment
In renally impaired patients (creatinine clearance < 10 ml/min) versus healthy subjects administered oral olanzapine, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hr) 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.

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 %).

Smoking
The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

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

## 5.3 Preclinical safety data

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.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Maltose
Citric acid monohydrate
Hydrochloric acid to adjust pH.

## 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Olanzapine for injection should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed.

Lorazepam injection should not be used to reconstitute olanzapine for injection as this combination results in a delayed reconstitution time.

Olanzapine for injection should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

## 6.3 Shelf life

Vial: 3 years
Solution (after reconstitution): 1 hour. Do not freeze.

## 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

## 6.5 Nature and contents of container

Type I glass vial with bromobutyl rubber stopper and aluminium flip cap.
One carton contains 1 or 10 vial(s).

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Reconstitute Ceyxa only with water for injections using standard aseptic techniques for reconstitution of parenteral products. No other solutions should be used for reconstitution (see section 6.2).

1. Withdraw 2.0 ml of water for injection into a sterile syringe. Inject into a vial of Ceyxa.
2. Rotate the vial until the contents have completely dissolved, giving a yellow-coloured solution. The vial contains 10.0 mg olanzapine as a solution of 5 mg/ml.

3. The following table provides injection volumes for delivering various doses of olanzapine:

| Dose (mg) | Volume of injection (ml) |
|---|---|
| 10 | 2.0 |
| 7.5 | 1.5 |
| 5 | 1.0 |
| 2.5 | 0.5 |

4. Administer the solution intramuscularly. Do not administer intravenously or subcutaneously.

5. Discard the syringe and any unused solution in accordance with appropriate clinical procedures.

6. Use the solution immediately within 1 hour of reconstitution.

Parenteral medicines should be inspected visually for particulate matter prior to administration.

## 7 MARKETING AUTHORISATION HOLDER

Nordic Pharma Limited,
Building 1410, Arlington Business Park
Theale, Reading
RG7 4SA
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

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## 10 DATE OF REVISION OF THE TEXT

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