# Olanzapine 2.5 mg tablets
# Olanzapine 5 mg tablets
# Olanzapine 7.5 mg tablets
# Olanzapine 10 mg tablets
# Olanzapine 15 mg tablets
# Olanzapine 20 mg tablets

## (olanzapine)

## PL 32854/0015-20

## UK Public Assessment Report

### TABLE OF CONTENTS

# Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets

# (olanzapine)

# PL 32854/0015-20

## LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Galenicum Health Marketing Authorisations (licences) for the medicinal products Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets (PL 32854/0015-20) on 4th July 2011. These are prescription-only medicines (POM).

The active ingredient, olanzapine, belongs to a group of medicines called antipsychotics. Olanzapine is used to treat 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such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, and becoming withdrawn.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.

Olanzapine is also used to treat a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. It is also a mood stabiliser that prevents further occurrences of the disabling high and low (depressed) extremes of mood associated with this condition.

Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets were considered to be generic versions of the reference products authorised in the European community, Zyprexa® 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg & 20 mg coated tablets (EU/1/96/022/), marketed by Eli Lilly Nederland BV, based on the data submitted by Galenicum Health.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets outweigh the risks; hence Marketing Authorisations have been granted.

# Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets

# (olanzapine)

# PL 32854/0015-20

## SCIENTIFIC DISCUSSION

## TABLE OF CONTENTS

# INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Galenicum Health Marketing Authorisations for the medicinal products Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets (PL 32854/0015-20) on 4th July 2011. These are prescription-only medicines (POM).

These are applications for Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets, submitted under Article 10.1 of Directive 2001/83/EC claiming to be generic medicinal products of the reference products authorised in the European community, Zyprexa® 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg & 20 mg coated tablets (EU/1/96/022/, Eli Lilly Nederland BV). The first authorisation for Zyprexa® coated tablets was granted on 27/09/1996 in the EU through a centralised procedure. The reference products have been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets are for use in adults only. Olanzapine is indicated for the treatment of schizophrenia. It is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is also indicated for the treatment of moderate to severe manic episode. In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1 of the Summary of Product Characteristics).

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 $5HT_{2A/2C}$, $5HT_3$, $5HT_6$; dopamine $D_1$, $D_2$, $D_3$, $D_4$, $D_5$; cholinergic muscarinic receptors $M_1$-$M_5$; $\alpha_1$ 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 $5HT_2$ than dopamine $D_2$ receptors and greater $5HT_2$ than $D_2$ 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.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Olanzapine 10 mg tablets, to that of the clinical reference product, Zyprexa® 10 mg coated tablets (Lilly Laboratories, Spain).

The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).It is not considered that these medicinal products represent any risk to the environment. These generic products will be used as substitute for the brand products. There is no reason to conclude that marketing of these products will change the overall use pattern of the existing market.

# PHARMACEUTICAL ASSESSMENT

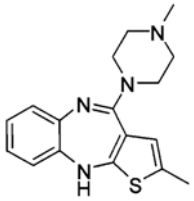
## ACTIVE SUBSTANCE

### Olanzapine

Nomenclature:

| | |
|---|---|
| INN: | Olanzapine |
| Chemical name: | 2-Methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine |

Structure:



| | |
|---|---|
| Molecular formula: | $C_{17}H_{20}N_4S$ |
| Molecular weight: | 312.44 g/mol |
| CAS No: | 132539-06-1 |
| Physical form: | A pale yellow to yellow crystalline powder |
| Solubility: | Freely soluble in chloroform and sparingly soluble in acetic acid |

The active substance, olanzapine, is not the subject of a European Pharmacopeia (Ph. Eur.) or British Pharmacopeia (B.P.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active substance are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer(s) during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated by the active substance manufacturers for active substance stored in packaging representative of the proposed commercial packaging. These data demonstrate the stability of the active substance and appropriate retest periods have been applied.

## MEDICINAL PRODUCT

### Description and Composition

Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets are presented as cylindrical or oblong-shaped (20 mg strength only), biconvex, yellow tablets, each containing 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg or 20 mg of the active ingredient, olanzapine.

Other ingredients consist of pharmaceutical excipients, namely magnesium stearate, crospovidone, microcrystalline cellulose and lactose monohydrate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

### Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic formulations, bioequivalent to the reference products, Zyprexa® 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg & 20 mg coated tablets (Eli Lilly Nederland BV).

Comparative dissolution and impurity data were provided for batches of the test and appropriate reference products. The dissolution and impurity profiles were satisfactory.

### Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory.

### Finished product specifications

Finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional

pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

### Container Closure System

Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets are licensed for marketing in aluminium-aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 28, 30, 56 or 100 tablets. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

### Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support shelf-lives of 3 years (for 2.5 mg, 5 mg, 7.5 mg and 10 mg strengths) and 30 months (for 15 mg and 20 mg strengths), with the storage instructions ‘Store in the original package’.

### Quality Overall Summary

A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

### Product Information

The approved Summaries of Product Characteristics (SmPCs), and Patient Information Leaflet (PIL) and labelling texts, are satisfactory. The user testing of the PIL text has been evaluated and is accepted. The labelling text fulfils the statutory requirements for Braille. The MAH has submitted text versions only and has committed to submitting mock-up livery to the MHRA for approval before packs are marketed.

### Conclusion

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets from a pharmaceutical point of view.

# PRE-CLINICAL ASSESSMENT

These abridged applications, submitted under Article 10.1 of Directive 2001/83/EC, as amended, are for Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets, products claiming to be generic versions of the reference products authorised in the European community, Zyprexa® 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg & 20 mg coated tablets (Eli Lilly Nederland BV).

No new pre-clinical data have been supplied with these applications and none are required for applications of this type. A pre-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

There are no objections to approval of these products from a pre-clinical point of view.

# CLINICAL ASSESSMENT

## BACKGROUND

Olanzapine, a thienobenzodiazepine derivative, belongs to the relatively new class of second-generation derivative antipsychotic agents, called atypical antipsychotics. Generally, those drugs that, in contrast to classical antipsychotics (e.g. haloperidol), have a greater affinity for serotonin 5-HT2A receptors than for dopamine D2 receptors, cause fewer extrapyramidal symptoms (EPS) and improve negative symptoms, are classified as atypical antipsychotics. The generic products under consideration have the same qualitative and quantitative composition, in terms of active substance, as the reference products.

## INDICATIONS

Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets are for use in adults only. Olanzapine is indicated for the treatment of schizophrenia. It is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is also indicated for the treatment of moderate to severe manic episode. In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1 of the Summary of Product Characteristics).

The indications are identical to those for the centrally approved reference products and are satisfactory.

## POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is identical to that for the centrally approved reference products and is satisfactory.

## TOXICOLOGY

The toxicology of olanzapine is well-known. No new data have been submitted and none are required for applications of this type.

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

The clinical pharmacology of olanzapine is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

### Pharmacokinetics - Bioequivalence study

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Olanzapine 10 mg tablets, to that of the clinical reference product sourced from Spain, Zyprexa® 10 mg coated tablets (Laboratorios Lilly). The Spanish brand leader tablets used in the bioequivalence study are equivalent to the UK brand leader since the product was community authorised. The study was of an appropriate design and was conducted to principles of

Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference products.

This was a comparative, randomised, open-label, two-period, two-sequence, two-way crossover, single-dose bioequivalence study conducted in 24 healthy, adult human subjects under fasting conditions. Following an overnight fast of at least 10 hours, a single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 14 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 144.0 hours after administration of test or reference products. Plasma levels of olanzapine were detected by a validated HPLC-MS/MS analytical method.

The primary pharmacokinetic parameters for this study were $C_{max}$, $AUC_{0-t}$, and $AUC_{0-72}$. Bioequivalence of the test product versus the reference products was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed $C_{max}$, $AUC_{0-t}$, and $AUC_{0-72}$.

Results

24 subjects were enrolled in the study and all 24 completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

*Safety* - There were no deaths or serious or significant adverse events.

A summary of the results of the bioequivalence study is tabulated below:

Pharmacokinetic results for olanzapine for a randomised, two-period, two-way crossover, single-dose bioequivalence study between the 10 mg strength test and reference products. n=24 healthy subjects, dosed fasted; t=144 hours. Wash-out period: 14 days.

| Pharmacokinetic parameters | Zyprexa® Mean (± SD) | Olanzapine 10 mg Mean (± SD) | Confidence intervals (90% CI) Transformed data |
|---|---|---|---|
| $AUC_{0-t}$ (ng×h/ml) | 668.54 ± 339.01 | 669.47 ± 386.85 | 86.7510 — 103.8245 |
| $AUC_{0-72}$ (ngxh/ml) | 503.88 ± 212.39 | 506.12 ± 238.74 | 89.9636 — 105.7379 |
| Cmax (ng/ml) | 17.401 ± 5.650 | 17.845 ± 6.144 | 96.9155 — 106.7354 |

| | |
|---|---|
| $C_{max}$ | maximum plasma concentration |
| $AUC_{0-t}$ | area under the plasma concentration-time curve from time zero to t hours |
| $AUC_{0-72}$ | area under the plasma concentration-time curve from time zero to 72 hours |

**Conclusion on Bioequivalence**

The results of the bioequivalence study show that the test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for $C_{max}$, $AUC_{0-t}$, and $AUC_{0-72}$ for olanzapine, fall within the acceptance criteria ranges of 80.00-125.00% in line with current guidelines.

Satisfactory justification is provided for a bio-waiver for Olanzapine 2.5 mg, 5 mg, 7.5 mg, 15 mg and 20 mg tablets. As Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets meet the criteria specified in the "Guideline on the Investigation of

Bioequivalence" (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 10 mg strength can be extrapolated to the 2.5 mg, 5 mg, 7.5 mg, 15 mg and 20 mg strength tablets.

## EFFICACY

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of olanzapine is well-established from its extensive use in clinical practice.

## SAFETY

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of olanzapine is well-known.

## PRODUCT INFORMATION:

### Summary of Product Characteristics

The approved SmPCs are fully harmonised with those for the reference products and are acceptable.

### Patient Information Leaflet

The final PIL text is in line with the approved SmPCs and is satisfactory.

### Labelling

The labelling text is satisfactory.

### Clinical overview

A satisfactory clinical overview was provided and was prepared by an appropriately qualified expert. The overview, dated January 2006, cites a comprehensive bibliography up to year 2006. The CV of the clinical expert was supplied.

## CONCLUSIONS

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended.

# OVERALL CONCLUSION AND BENEFIT- RISK ASSESSMENT

## QUALITY

The important quality characteristics of Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

## PRE-CLINICAL

No new pre-clinical data were submitted and none are required for applications of this type.

## CLINICAL

Bioequivalence has been demonstrated between the applicant's Olanzapine 10 mg tablets, and the clinical reference product, Zyprexa® 10 mg coated tablets (Laboratorios Lilly, Spain)

As the proposed products, Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets, meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 10 mg strength were extrapolated to the 2.5 mg, 5 mg, 7.5 mg, 15 mg & 20 mg strength tablets, and omission of further bioequivalence studies on the other strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

## PRODUCT LITERATURE

The approved SmPCs are consistent with those for the reference products and are satisfactory.

The PIL text is in line with the SmPCs and is satisfactory. The leaflet text has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the leaflet text meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling texts are satisfactory and fulfil the statutory requirements for Braille. The MAH has submitted text versions only for the PIL and labelling, and has committed to submitting mock-up livery to the MHRA for approval before packs are marketed.

## BENEFIT- RISK ASSESSMENT

The quality of the products is acceptable and no new pre-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant's Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets are generic versions of the centrally authorised reference products, Zyprexa® 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg & 20 mg coated tablets (Eli Lilly Nederland BV). Extensive clinical experience with olanzapine is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.

# Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets

# (olanzapine)

# PL 32854/0015-20

## STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation applications on 5th February 2010.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 16th February 2010.

3 Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 25th June 2010 and further information relating to the quality dossier on 30th June 2010.

4 The applicant responded to the MHRA's requests, providing further information for the clinical and quality sections on 10th September 2010.

5 The applications were determined on 4th July 2011.

# Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets

# (olanzapine)

# PL 32854/0015-20

## STEPS TAKEN AFTER AUTHORISATION

Not applicable

# SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets (PL 32854/0015-20) is as follows. Differences between the individual SmPCs are highlighted:

## 1 NAME OF THE MEDICINAL PRODUCT

Olanzapine 2.5 mg tablets.
Olanzapine 5 mg tablets.
Olanzapine 7.5 mg tablets.
Olanzapine 10 mg tablets.
Olanzapine 15 mg tablets.
Olanzapine 20 mg tablets.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5/5/7.5/10/15/20 mg olanzapine.

Excipient: 16.34/32.68/49.02/65.36/98.04/130.72 mg anhydrous lactose per tablet.
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet
Olanzapine 2.5 mg tablets are yellow, cylindrical, biconvex tablets.
Olanzapine 5 mg tablets are yellow, cylindrical, biconvex tablets.
Olanzapine 7.5 mg tablets are yellow, cylindrical, biconvex tablets.
Olanzapine 10 mg tablets are yellow, cylindrical, biconvex tablets.
Olanzapine 15 mg tablets are yellow, cylindrical, biconvex tablets.
Olanzapine 20 mg tablets are yellow, oblongs, biconvex tablets.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adults*

Olanzapine is indicated for the treatment of schizophrenia.

Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is indicated for the treatment of moderate to severe manic episode.

In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1).

### 4.2 Posology and method of administration

*Adults*

Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.

Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in combination therapy (see section 5.1).

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

During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20 mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours. Olanzapine can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

*Paediatric population*

Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short term studies of adolescent patients than in studies of adult patients (see sections 4.4, 4.8, 5.1 and 5.2).

*Elderly*

A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant (see section 4.4).

*Renal and/or hepatic impairment*

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

*Gender*

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

*Smokers*

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

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

(See sections 4.5 and 5.2)

**4.3 Contraindications**

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

**4.4 Special warnings and precautions for use**

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

*Dementia-related psychosis and/or behavioural disturbances*

Olanzapine is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients 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 product. 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 rarely, 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. Patients treated with any antipsychotic agents, including olanzapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

*Lipid alterations*

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 agents, including olanzapine, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines.

*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 (see section 4.8).

*Discontinuation of treatment*

Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely (<0.01%) when olanzapine is stopped abruptly.

*QT interval*

In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post baseline in patients with baseline QTcF<500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. However, as with other antipsychotics, 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*

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Olanzapine and preventive measures undertaken.

*General CNS activity*

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

*Seizures*

Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely 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. As with other antipsychotics, 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. Long-term outcomes associated with these events have not been studied and remain unknown (see sections 4.8 and 5.1).

*Lactose*

Olanzapine tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

*Paediatric population*

Interaction studies have only been performed in adults.

*Potential interactions affecting olanzapine*

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

*Induction of CYP1A2*

The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. 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 non-smokers and 77 % in male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

*Decreased bioavailability*

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

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

*Potential for olanzapine to affect other medicinal products*

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

Olanzapine does not inhibit the main CYP450 isoenzymes in vitro (e.g. 1A2, 2D6, 2C9, 2C19, 3A4). Thus no particular interaction is expected as verified through in vivo studies where no inhibition of metabolism of the following active substances was found: tricyclic antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19).

Olanzapine showed no interaction when co-administered with lithium or biperiden.

Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.

*General CNS activity*

Caution should be exercised in patients who consume alcohol or receive medicinal products that can cause central nervous system depression.

The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended (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 Pregnancy and lactation

*Pregnancy*

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

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

*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.

## 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

*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 (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases (see section 4.4), rash, asthenia, fatigue and oedema.

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 (≥10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

| Very common | Common | Uncommon | Not known |
|---|---|---|---|
| **Blood and the lymphatic system disorders** | | | |
| | Eosinophilia | Leukopenia<br>Neutropenia | Thrombocytopenia |
| **Immune system disorders** | | | |
| | | | Allergic reaction |
| **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)<br>Hypothermia |
| **Nervous system disorders** | | | |
| Somnolence | Dizziness<br>Akathisia[6]<br>Parkinsonism6 Dyskinesia[6] | | Seizures where in most cases a history of seizures or risk factors for seizures were reported<br>Neuroleptic malignant syndrome (see section 4.4)<br>Dystonia (including oculogyration)<br>Tardive dyskinesia<br>Discontinuation symptoms[7] |
| **Cardiac disorders** | | | |
| | | Bradycardia<br>QTc prolongation (see section 4.4) | Ventricular tachycardia/fibrillation, sudden death (see section 4.4) |
| **Vascular disorders** | | | |
| | Orthostatic hypotension | | Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs- Frequency unknown |
| **Gastrointestinal disorders** | | | |
| | Mild, transient anticholinergic effects including constipation and dry mouth | | Pancreatitis |

| | | | |
|---|---|---|---|
| **Hepato-biliary disorders** | | | |
| | Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4) | | Hepatitis (including hepatocellular, cholestatic or mixed liver injury) |
| **Skin and subcutaneous tissue disorders** | | | |
| | Rash | Photosensitivity reaction<br>Alopecia | |
| **Musculoskeletal and connective tissue disorders** | | | |
| | | | **Rhabdomyolysis** |
| **Renal and urinary disorders** | | | |
| | | Urinary incontinence | Urinary hesitation |
| **Reproductive system and breast disorders** | | | |
| | | | Priapism |
| **General disorders and administration site conditions** | | | |
| | Asthenia<br>Fatigue<br>Oedema | | |
| **Investigations** | | | |
| Elevated plasma prolactin levels8 | | High creatine phosphokinase<br>Increased total bilirubin | Increased alkaline phosphatase |

[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 can not 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. Generally in olanzapine-treated patients potentially associated breast- and menstrual related clinical manifestations (e.g. amenorrhoea, breast enlargement, galactorrhea in females, and gynaecomastia/breast enlargement in males) were uncommon. Potentially associated sexual function-related adverse reactions (e.g. erectile dysfunction in males and decreased libido in both genders) were commonly observed.

*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 also 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.

*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 (≥ 10%), common (≥ 1% and < 10%).

| |
|---|
| **Metabolism and nutrition disorders**<br>*Very common:* Weight gain[9], elevated triglyceride levels[10], increased appetite.<br>*Common:* Elevated cholesterol levels[11] |
| **Nervous system disorders**<br>*Very common:* Sedation (including: hypersomnia, lethargy, somnolence). |
| **Gastrointestinal disorders**<br>*Common:* Dry mouth |
| **Hepato-biliary disorders**<br>*Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4). |
| **Investigations**<br>*Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[12]. |

[9] 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.

[10] 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).

[11] 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.

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

## 4.9 Overdose

*Signs and symptoms*

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

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

*Management of overdose*

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

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

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diazepines, oxazepines and thiazepines, 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; α1 adrenergic; and histamine H1 receptors. Animal behavioral studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5HT2 than dopamine D2 receptors and greater 5 HT2 than D2 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 HT2A than dopamine D2 receptor occupancy. In addition, a SPECT imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

In two of two placebo and two of three comparator controlled trials with 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 olanzapine (-6.0) versus haloperidol (-3.1).

In patients with a manic or mixed episode of bipolar disorder, olanzapine demonstrated superior efficacy to placebo and valproate semisodium (divalproex) in reduction of manic symptoms over 3 weeks. 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 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.

*Paediatric population*

The experience in adolescents (ages 13 to 17 years) is limited to short term efficacy data in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no data on maintenance of effect and limited data on long term safety (see sections 4.4 and 4.8).

## 5.2 Pharmacokinetic properties

Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food. Absolute oral bioavailability relative to intravenous administration has not been determined.

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

In female versus male subjects the mean elimination half life was somewhat prolonged (36.7 versus 32.3 hr) 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).

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 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.

In smoking subjects with mild hepatic dysfunction, mean elimination half-life (39.3 hr) was prolonged and clearance (18.0 l/hr) was reduced analogous to non-smoking healthy subjects (48.8 hr and 14.1 l/hr, respectively).

In non-smoking versus smoking subjects (males and females) 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).

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.

The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-acid-glycoprotein.

*Paediatric population*

Adolescents (ages 13 to 17 years): The pharmacokinetics of olanzapine are similar between adolescents and adults. In clinical studies, the average olanzapine exposure was approximately 27% higher in adolescents. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers. Such factors possibly contribute to the higher average exposure observed in adolescents.

## 5.3 Preclinical safety data

*Acute (single-dose) toxicity*

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

*Repeated-dose toxicity*

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

*Haematologic toxicity*

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

*Reproductive toxicity*

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

*Mutagenicity*

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

*Carcinogenicity*

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

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Lactose monohydrate
Crospovidone
Microcrystalline cellulose
Magnesium stearate

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

For PLs PL 32854/0015-18: 3 years.
For PLs PL 32854/0019-20: 30 months.

**6.4 Special precautions for storage**

Store in the original package.

**6.5 Nature and contents of container**

Blister packs of 28, 30, 56 or 100 tablets in Aluminium/ aluminium blister.

*Not all pack sizes may be marketed.*

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Galenicum Health
S.L Avda/Diagonal 538 4º 1ª
08006 Barcelona
Spain

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 32854/0015
PL 32854/0016
PL 32854/0017
PL 32854/0018
PL 32854/0019
PL 32854/0020

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

04/07/2011

**10 DATE OF REVISION OF THE TEXT**

04/07/2011

# PATIENT INFORMATION LEAFLET - text

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**
**olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg tablets**
**olanzapine**

**Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**



## 1. WHAT OLANZAPINE IS AND WHAT IT IS USED FOR

Olanzapine belongs to a group of medicines called antipsychotics.

Olanzapine is used to treat 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.

Olanzapine is used to treat a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. It is also a mood stabiliser that prevents further occurrences of the disabling high and low (depressed) extremes of mood associated with this condition.

## 2. BEFORE YOU TAKE OLANZAPINE

**Do not take olanzapine:**

- If you are allergic (hypersensitive) to olanzapine or to any of the other ingredients of olanzapine tablets. An allergic reaction can be recognised as rash, itching, a swollen o face, swollen lips, or shortness of breath. If this happened to you, tell your doctor.
- If you have been previously diagnosed with eye problems such as certain kinds of glaucoma (increased pressure in the eye).

**Take special care with olanzapine:**

- 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.
- Medicines of this type may cause unusual movements mainly of the face or tongue. If this happens after you have been given olanzapine tell your doctor.
- Very rarely, medicines of this type cause a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness. If this happens, contact your doctor at once.

- The use of olanzapine in elderly patients with dementia is not recommended as it may have serious side effects.

If you suffer from any of the following illnesses tell your doctor as soon as possible:
• Diabetes
• Heart disease
• Liver or kidney disease
• Parkinson's disease
• Epilepsy
• Prostate problems
• A blocked intestine (Paralytic ileus)
• Blood disorders
• Stroke or "mini" stroke (temporary symptoms of stroke)

If you suffer from dementia, you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

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

Olanzapine is not for patients who are under 18 years.

**Taking other medicines:**

- Only take other medicines while you are on olanzapine if your doctor tells you that your can. You may feel drowsy if olanzapine is taken in combination with antidepressants or medicines taken for anxiety or to help you sleep (tranquillisers).
- You should tell your doctor if you are taking fluvoxamine (an antidepressant) or ciprofloxacin (an antibiotic), as it may be necessary to change your olanzapine dose.
- Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Especially tell your doctor if you are taking medicines for Parkinson's disease.

**Taking olanzapine with food and drink:**
Do not drink any alcohol while you have been given olanzapine as olanzapine and alcohol together may make you feel drowsy.

**Pregnancy and breast-feeding:**

Tell your doctor as soon as possible if you are pregnant or think you may be pregnant. You should not take this medicine when pregnant, unless you have discussed this with your doctor. You should not be given this medicine when breast-feeding, as small amounts of olanzapine can pass into breast milk.

**Driving and using machines:**
There is a risk of feeling drowsy when you are given olanzapine. If this happens, do not drive or operate any tools or machines. Tell your doctor.

**Important information about some of the ingredients of olanzapine:**

This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. HOW TO TAKE olanzapine

- Always take olanzapine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- Your doctor will tell you how many olanzapine to take and how long you should continue to take them. The daily dose of olanzapine is between 5 and 20 mg. Consult your doctor if your symptoms return but do not stop taking olanzapine unless your doctor tells you to.
- You should take your olanzapine once a day following the advice of your doctor. Try to take your tablets at the same time each day. It does not matter whether you take them with or without food. Olanzapinetablets are for oral use. You should swallow the olanzapine tablets whole with water.

### If you take more olanzapine than you should:

Patients who have taken more olanzapine than they should, have 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 be: acute confusion, seizures (epilepsy), coma, a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness, slowing of the breathing rate, aspiration, high blood pressure or low blood pressure, abnormal rhythms of the heart. Contact your doctor or hospital straight away. Show the doctor your pack of tablets.

### If you forget to take olanzapine:

Take your tablet as soon as you remember it. Do not take two doses in one day.

### If you stop taking olanzapine:

Do not stop taking your tablets just because you feel better. It is important that you carry on taking olanzapine for as long as your doctor tells you.
If you suddenly stop taking olanzapine, symptoms such as sweating, unable to sleep, tremor, anxiety or nausea and vomiting might occur. Your doctor may suggest you to reduce the dose gradually before stopping treatment.

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

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, olanzapine can cause side effects, although not everybody gets them.
Very common side effects: affect 1 user in 10

- Weight gain.
- Sleepiness.
- Increases in the levels of prolactin in the blood.

Common side effects: affect 1 to 10 users in 100

- Changes in the levels of some blood cells and circulating fats.
- Increases in the level of sugars in the blood and urine.

- Feeling more hungry.
- Dizziness.
- Restlessness.
- Tremor.
- Muscle stiffness or spasm (including eye movements).
- Problems with speech.
- Unusual movement (especially of the face or tongue).
- Constipation.
- Dry mouth.
- Rash.
- Loss of strength.
- Extreme tiredness.
- Water retention leading to swelling of the hands, ankles or feet.
- 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.
- Sexual dysfunctions such as decreased libido in males and females or erectile dysfunction in males.

Uncommon side effects: affect 1 to 10 users in 1,000

- Slow heart rate.
- Make you sensitive to sunlight.
- Urinary incontinence.
- Hair loss.
- Absence or decrease in menstrual periods.
- Changes in breasts in males and females such as an abnormal production of breast milk or abnormal growth.

Other possible side effects: frequency cannot be estimated from the available data.

- Allergic reaction (e.g. swelling in the mouth and throat, itching, rash).
- Blood clots in the veins 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.
- Diabetes or the worsening of diabetes, occasionally associated with ketoacidosis (ketones in the blood and urine) or coma.
- Lowering of normal body temperature.
- Seizures, usually associated with a history of seizures (epilepsy).
- Combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness.
- Spasms of the muscle of the eye causing rolling movement of the eye.
- Abnormal rhythms of the heart.

- Sudden unexplained death.
- Blood clots such as deep venous thrombosis of the leg or blood clot on the lung.
- 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.
- Difficulty in passing urine.
- Prolonged and/or painful erection.

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 olanzapine may worsen the symptoms.

Rarely women taking medicines of this type for a long time have started to secrete milk and have missed periods or had irregular periods. If this persists tell your doctor. Very rarely babies born to mothers who have taken olanzapine in the last stage of pregnancy (3rd trimester) may have tremors, be sleepy or drowsy.

Blood clots in the veins 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.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE OLANZAPINE

Keep out of the reach and sight of children.

Do not use olanzapine after the expiry date which is stated on the carton.

Store in the original package.

Please return left over medicine to your pharmacist. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What olanzapine contains

The active substance is olanzapine. Each olanzapine tablet contains either 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg or 20 mg of the active substance.
The other ingredients are: Microcrystalline cellulose, anhydrous lactose, crospovidone, magnesium stearate.

### What olanzapine looks like and contents of the pack

Olanzapine is supplied in the form of tablets.

Description: Olanzapine 2,5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg tablets are yellow, cylindrical and biconvex.

Olanzapine 20 mg tablets are yellow, oblong and biconvex.

Olanzapine tablets are available in 28, 30, 56 and 100 tablets packs.

**Marketing Authorisation Holder and Manufacturer**

*Marketing Authorisation Holder:*
Galenicum Health, S.L.
Avda/Diagonal 538 4º 1ª, 08006 Barcelona, Spain

*Manufacturer:*
Laboratorios Cinfa, S.A.
C/ Olaz-Chipi, 10 – Polígono Industrial Areta 31620 Huarte-Pamplona (Navarra) – Spain

**This leaflet was last approved in month/year**

# LABELLING - text

The MAH has submitted text versions only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed. The labelling text is identical for all the tablets apart from the strength and PL number.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON OF 28/30/56/100 TABLETS IN BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine 2.5/5/7.5/10/15/20 mg tablets
Olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5/5/7.5/10/15/20 mg of olanzapine.

3. LIST OF EXCIPIENTS

This product also contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

28/30/56/100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be taken as directed by your doctor.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

| 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
|---|

Galenicum Health, S.L.
Avda/Diagonal 538 4º 1ª
08006 Barcelona
Spain

| 12. MARKETING AUTHORISATION NUMBER(S) |
|---|

*32854/0015*
*32854/0016*
*32854/0017*
*32854/0018*
*32854/0019*
*32854/0020*

| 13. BATCH NUMBER |
|---|

Lot

| 14. GENERAL CLASSIFICATION FOR SUPPLY |
|---|

Medicinal product subject to medical prescription.
POM

| 15. INSTRUCTIONS ON USE |
|---|

| 16. INFORMATION IN BRAILLE |
|---|

olanzapine 2.5/5/7.5/10/15/20 mg tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
BLISTER FOIL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine 2.5/5/7.5/10/15/20 mg tablets
Olanzapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Galenicum Health, S.L.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER