Public Assessment Report

Decentralised Procedure

OLANZAPINE 5MG ORODISPERSIBLE TABLETS
OLANZAPINE 10MG ORODISPERSIBLE TABLETS
OLANZAPINE 15MG ORODISPERSIBLE TABLETS
OLANZAPINE 20MG ORODISPERSIBLE TABLETS

Procedure No: UK/H/1387/001-4/DC

UK Licence No: PL 30306/0348-51

ACTAVIS GROUP PTC EHF
LAY SUMMARY

In May 2010, the MHRA granted Sigillata Limited Marketing Authorisations (licences) for the medicinal products Olanzapine 5, 10, 15 and 20mg Orodispersible Tablets (PL 30130/0010-3; UK/H/1387/001-4/DC). These products were granted via the decentralised procedure, with the UK as reference member state (RMS) and Belgium, Bulgaria, Greece, Ireland, Italy, the Netherlands, Romania, Spain and Sweden as concerned member states (CMS). These are prescription-only medicines (POM). These licences underwent a change of ownership to Actavis Group PTC ehf on 09 March 2011.

Olanzapine 5mg, 10mg, 15 mg & 20mg Orodispersible Tablets contain the active ingredient, olanzapine, which belongs to a group of medicines called antipsychotics and is used to treat the symptoms of schizophrenia. Such symptoms include hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness and becoming withdrawn.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 conditions 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 irritability. It acts as a mood stabilizer that prevents further occurrences of these disabling high and low extremes of mood associated with these conditions.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Olanzapine Orodispersible Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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## Module 1

<table>
<thead>
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<th>Olanzapine 5mg, 10mg, 15mg and 20mg Orodispersible Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Olanzapine</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Orodispersible Tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>5, 10, 15 and 20mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Actavis Group PTC ehf, Reykjavikurvegur 76-78, Hafnarfjordur, IS-220, Iceland.</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>UK/H/1387/001-4/DC: Belgium, Bulgaria, Greece, Ireland, Italy, the Netherlands, Romania, Spain and Sweden</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1387/001-4/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 21st April 2010</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

The current approved UK version of the Summary of Product Characteristics (SmPC) for these products is available on the MHRA website.
Module 3
Patient Information Leaflet

The current approved UK version of the Patient Information Leaflet (PIL) for these products is available on the MHRA website.
5 mg Blister:
PAR Olanzapine Orodispensible Tablets UK/II/1387/001-4/DC

10 mg Carton:
15 mg Blister:
15 mg Carton:
20 mg Blister:
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
In May 2010, the MHRA granted Sigillate Limited Marketing Authorisations (licences) for the medicinal products Olanzapine 5, 10, 15 and 20mg Orodispersible Tablets (PL 30130/0010-3; UK/H/1387/001-4/DC). These products were granted via the decentralised procedure (Day 210 – 21st April 2010), with the UK as reference member state (RMS) and Belgium, Bulgaria, Greece, Ireland, Italy, the Netherlands, Romania, Spain and Sweden as concerned member states (CMS). These licences underwent a change of ownership to Actavis Group PTC ehf on 09 March 2011.

These are prescription-only medicines (POM) for the treatment of schizophrenia, moderate to severe manic episodes and bipolar disorder.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Zyprexa 5mg, 10mg, 15mg and 20mg Coated Tablets, which were originally granted licences to Eli Lilly Nederland BV in September 1996.

The products contain the active ingredient olanzapine, which is a second-generation “atypical” antipsychotic indicated for the treatment of schizophrenia, manic episodes and preventing recurrence in bipolar disorder. The starting dose is 10 mg/day for the treatment of schizophrenia and preventing recurrence in bipolar disorder and 15 mg/day (single dose in monotherapy) for treatment of manic episodes.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Olanzapine 5mg, 10mg, 15mg and 20mg Orodispersible Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antipsychotics (N05A H03)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>5mg, 10mg, 15mg and 20mg Orodispersible Tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1387/001-4/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>UK/H/1387/001-4/DC: Belgium, Bulgaria, Greece, Ireland, Italy, the Netherlands, Romania, Spain and Sweden</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 30130/0010-3</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Actavis Group PTC ehf, Reykjavikurvegur 76-78, Hafnarfjordur, IS-220, Iceland.</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Olanzapine
Chemical Name: 2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine
Molecular Formula: C_{17}H_{20}N_{4}S

Chemical Structure:

![Chemical Structure Image]

Molecular Weight: 312.44
Appearance: A pale yellow to yellow crystalline powder, freely soluble in chloroform and sparingly soluble in acetic acid

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients magnesium stearate, L-methionine, silica colloidal anhydrous, hydroxypropyl cellulose low substituted, crospovidone, aspartame, microcrystalline cellulose, guar gum, magnesium carbonate heavy and orange flavour.

With the exception of the orange flavour and guar gum, all excipients comply with their respective European Pharmacopoeia monograph. Both orange flavour and guar gum comply with their respective in-house specifications, which are satisfactory.
None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The objective of the development programme was to formulate robust, stable tablets that contain qualitatively and quantitatively the same active ingredient as Zyprexa 5mg, 10mg, 15mg and 20mg Coated Tablets (Eli Lilly Nederland BV), and exhibiting the same bioavailability in order to comply with the regulations pertaining to generic medicinal product applications.

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and originator products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**
The finished product specifications proposed for all strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**
All strengths of tablets are packaged in either

1. oriented polyamide/aluminium/polyvinylchloride “push-through” blister packs in pack sizes of 28, 35 56 and 70 tablets.
2. paper/polyethylene terephthalate/aluminium “peel-to-open” blister packs, in pack sizes of 28, 35 56 and 70 tablets.

It has been stated that not all pack sizes may be marketed. However, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with the storage instructions “Store in the original package in order to protect from light and moisture”.

Suitable post approval stability commitments have been provided.
Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of olanzapine are well-known, no further preclinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of a detailed environmental risk assessment.

There are no objections to the approval of these products from a preclinical viewpoint.
III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, three-period, two-treatment, three-sequence, single-dose, three-way crossover study to compare the pharmacokinetics of the test product Olanzapine 5mg Orodispersible Tablets versus the reference products Zyprexa Olanzapin 5mg Filmtabletten (Eli Lilly Nederland BV) and Zyprexa Velotab 5mg Schmelztabletten (Eli Lilly Nederland BV) in healthy volunteers under fasting conditions.

Volunteers received the test or reference treatment after an overnight fast of at least 10 hours and fasted for at least 5 hours thereafter. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 144 hours post dose. The three treatment arms were separated by a 21-day washout period.

The log-transformed pharmacokinetic results for olanzapine are presented below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\text{0-t}</th>
<th>AUC\text{0-}\infty</th>
<th>C\text{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (Olanzapine 5mg Orodispersible Tablets)</td>
<td>12.48 (0.28)</td>
<td>12.55 (0.29)</td>
<td>8.80 (0.30)</td>
</tr>
<tr>
<td>Reference 1 (Zyprexa Olanzapin 5mg Filmtabletten)</td>
<td>12.50 (0.27)</td>
<td>12.57 (0.28)</td>
<td>8.85 (0.37)</td>
</tr>
<tr>
<td>Reference 2 (Zyprexa Velotab 5mg Schmelztabletten)</td>
<td>12.51 (0.29)</td>
<td>12.58 (0.29)</td>
<td>8.83 (0.30)</td>
</tr>
<tr>
<td>Ratio (90% CI) Test Vs Reference 1</td>
<td>0.98 (0.95-1.02)</td>
<td>0.98 (0.95-1.02)</td>
<td>0.95 (0.90-1.01)</td>
</tr>
<tr>
<td>Ratio (90% CI) Test Vs Reference 2</td>
<td>0.97 (0.94-1.01)</td>
<td>0.98 (0.94-1.01)</td>
<td>0.98 (0.93-1.04)</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for $C\text{max}$ and AUC for test product versus reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference products.

As the 5, 10, 15 and 20mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the extrapolation of results and conclusions from the bioequivalence study on the 5mg strength to the other strengths is justified.

Efficacy
No new data on the efficacy have been submitted and none are required for these types of applications.

Safety
No new or unexpected safety issues were raised by the bioequivalence data.

SPC, PIL, Labels
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.
Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfills the requirements and provides adequate evidence that the applicant has the services of a qualified person 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.

A suitable justification has been provided for not submitting a risk management plan for these products.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA forms
The MAA forms are medically satisfactory.

Conclusion
The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Olanzapine 5, 10, 15 and 20mg Orodispersible 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 risk-benefit balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Olanzapine 5mg Orodispersible Tablets and the respective reference products. As the 5, 10, 15 and 20mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 5mg strength can be extrapolated to the other strengths of tablet.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with olanzapine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/03/2013</td>
<td>Type 1B</td>
<td>To update sections 3, 4.2, 4.3, 4.4, 4.8, 4.9, 5.1 and 5.2 of the Summary of Product Characteristics (SmPC) in line with the reference product SmPC for 'Zyprexa Velotab orodispersible tablets'. Consequently the patient information leaflet (PIL) has been updated. The wording of the child safety warning on the labels has been updated in line with the latest QRD template.</td>
<td>Granted 07/06/2013</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL 30306/0348-0022
          PL 30306/0349-0021
          PL 30306/0350-0021
          PL 30306/0351-0020

Product: Olanzapine 5mg Orodispersible Tablets
         Olanzapine 10mg Orodispersible Tablets
         Olanzapine 15mg Orodispersible Tablets
         Olanzapine 20mg Orodispersible Tablets

Marketing Authorisation Holder: Actavis Group PTC ehf
Active Ingredient(s): Olanzapine

Reason
To update sections 3, 4.2, 4.3, 4.4, 4.8, 4.9, 5.1 and 5.2 of the Summary of Product Characteristics (SmPC) in line with the reference product SmPC for 'Zy prexa Velotab orodispersible tablets'. Consequently the patient information leaflet (PIL) has been updated.
The wording of the child safety warning on the labels has been updated in line with the latest QRD template.

Supporting evidence
Revised SmPC, PIL text and label mock-ups have been provided.

Evaluation
Satisfactory updated SmPC fragments, PIL and labels were submitted in support of the variation applications.

Conclusion
The amendments to the SmPC fragments, leaflet and labels can be approved.

In accordance with Directive 2010/84/EU, the SmPCs and PILs for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision: Approved on 7 June 2013.