Public Assessment Report

Decentralised Procedure

Azithromycin 250 mg and 500 mg Film-coated Tablets

(Azithromycin anhydrous)

UK/5111/001-02/DC

UK licence no: PL 29831/0537 & 0512

Wockhardt UK Limited
LAY SUMMARY

On 18th July 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) to Wockhardt UK Ltd for the medicinal products Azithromycin 250 mg and 500 mg Film-coated Tablets (PL 29831/0537 and 0512, UK/H/5111/001-02/DC). These are prescription-only medicines (POM).

Azithromycin is one of a group of antibiotics called macrolides. It is used to treat infections caused by certain bacteria and other micro-organisms, which include:

- Chest, throat or nasal infections (such as acute worsening of chronic bronchitis, pneumonia, tonsillitis, sore throat (pharyngitis and sinusitis)
- Ear infections
- Skin and soft tissue infections (such as an abscess or boil)
- Sexually transmitted diseases caused by an organism called Chlamydia.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Azithromycin 250 mg and 500 mg Film-coated Tablets outweigh the risks. Hence Marketing Authorisations have been granted.
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# Module 1

<table>
<thead>
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<th><strong>Product Name</strong></th>
<th>Azithromycin 250 mg and 500 mg Film-coated Tablets</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
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<td><strong>Active Substance</strong></td>
<td>Azithromycin anhydrous</td>
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<tr>
<td><strong>Form</strong></td>
<td>Film-coated Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>250 mg and 500 mg Film-coated Tablets</td>
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</tbody>
</table>
| **MA Holder** | Wockhardt UK Ltd  
Ash Road North  
Wrexham  
LL13 9UF  
UK |
| **RMS** | UK |
| **CMS** | Cyprus and Republic of Ireland |
| **Procedure Numbers** | UK/H/5111/001-02/DC |
| **Timetable** | Day 210 – 10th July 2013 |
Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3

PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Azithromycin 250 mg and 500 mg Film-coated Tablets for the treatment of the following bacterial infections induced by micro-organisms susceptible to azithromycin could be approved:

- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Skin and soft tissue infections
- uncomplicated Chlamydia trachomatis urethritis and cervicitis

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended for Azithromycin 250 mg and 500 mg Film-coated Tablets. The European reference product is Azithromax 500 mg Film-coated Tablets granted to Pfizer A.B, Sweden on 2nd August 1995. The UK reference product are Zithromax 250 mg and 500 mg tablets (PL 00057/0335 and PL 00057/0391), granted to Pfizer Ltd on 4th April 1991 and 17th September 1996, respectively.

With UK as the RMS in these Decentralised Procedures (UK/H/5111/001-02/DC), Wockhardt UK Ltd applied for the Marketing Authorisations for Azithromycin 250 mg and 500 mg Film-coated Tablets in Cyprus and Republic of Ireland.

No new non-clinical or 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.

A bioequivalence study (single-dose) was submitted to support these applications, comparing the applicant’s test product Azithromycin 500 mg Tablets (Wockhardt Ltd, India) with the reference product Zithromax™ 500 mg Tablets (Pfizer Pharma, Berlin). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those...
countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and 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 for non-submission of a Risk Management Plan has been provided.

All member states agreed to grant licences for the above products at the end of procedure (Day 210 – 10th July 2013). After a subsequent national phase, the UK granted licences for these products on 18th July 2013 (PL 29831/0537 & 0512).
### II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Azithromycin 250 mg and 500 mg Film-coated Tablets</th>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Azithromycin anhydrous</td>
</tr>
<tr>
<td>Pharmacotherapeutical classification (ATC code)</td>
<td>Group: Antibacterials for systemic use, macrolides ATC Code: J01FA10</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Film-coated Tablet, 250 mg and 500 mg</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedures</td>
<td>UK/H/5111/001-02/DC</td>
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<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States</td>
<td>Cyprus and Republic of Ireland</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 29831/0537 &amp; 0512</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Wockhardt UK Ltd</td>
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<tr>
<td></td>
<td>Ash Road North</td>
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<tr>
<td></td>
<td>Wrexham</td>
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<td></td>
<td>LL13 9UF</td>
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<td></td>
<td>UK</td>
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</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
DRUG SUBSTANCE

INN: Azithromycin anhydrous

Chemical Names: (2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 14R)-13-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[(3,4,6-rideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

Structure:

Molecular Formula: C₃₈H₇₂N₂O₁₂

Molecular Weight: 749 g/mol

Appearance: white to off-white amorphous powder

Solubility: It is practically insoluble in water, freely soluble in anhydrous ethanol and methylene chloride

Azithromycin anhydrous is the subject of an Active Substance Master File (ASMF). A satisfactory letter of access has been provided.

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 drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.
DRUG PRODUCT

Other Ingredients
Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, maize starch, croscarmellose sodium, magnesium trisilicate (E553a), magnesium stearate, colloidal silicon dioxide (E551), hydroxypropyl cellulose (E463), sodium lauryl sulphate making up the tablet core; and film-coat consisting of Opadry Y-1-7000 white (hypromellose (E464), titanium dioxide (E171) and polyethylene glycol 400).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry Y-1-7000 white which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has confirmed that the magnesium stearate used in the tablets is of vegetable origin.

Pharmaceutical Development
The objective of the development programme was to formulate robust, stable tablets that could be considered generic medicinal products of the innovator’s product Zithromycin 500 mg Tablets (Pfizer Limited).

Comparative impurity and dissolution profiles have been presented for the test and reference products.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packed in aluminium/polyvinylchloride blister packs in a cardboard carton. Pack sizes of 2, 3, 4, 6, 9, 12 and 24 film-coated tablets (for 250 mg) and 2 and 3 film-coated tablets (for 500 mg).

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months with no special storage conditions has been set. These are satisfactory.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labels are pharmaceutically acceptable.

User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for Donepezil Hydrochloride 5 mg and 10 mg Film-coated Tablets (PL 29831/0440-0441). These leaflets have identical layout and format. The justification on the rationale for bridging is accepted.

The Marketing Authorisation Holder has committed to submit mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

Expert report/Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of azithromycin anhydrous are well known.

No new non-clinical data have been supplied with these applications and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of an environmental risk assessment. This was satisfactory.

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

III.3 CLINICAL ASPECTS
Clinical Pharmacology
Pharmacokinetics
In support of these applications, the following bioequivalence study has been submitted:

This is an open label randomised, two-treatment, two-sequence, two-period, two-way crossover, single-dose comparative oral bioavailability study of Azithromycin 500 mg Tablets (Wockhard Ltd, India) versus the reference product Zithromax™ (containing Azithromycin) 500 mg Tablets (Pfizer Pharma, Berlin K) in healthy adult male subjects under fasting condition.

Twenty blood samples were taken pre-dose and at 0.50, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.5, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 24.00, 48.00 and 72.00 hours after administration of the products. There was a washout period of 21 days between study drug administrations.
**Geometric Means, Ratios and 90% Confidence Interval for Azithromycin (n=54) on Log transformed Data**

<table>
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<tr>
<th>Parameter (Units)</th>
<th>Geometric Least Squares Mean</th>
<th>90% Confidence Interval</th>
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<tr>
<td></td>
<td>N=54</td>
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<tr>
<td>Test (A)</td>
<td>Reference (B)</td>
<td>% Ratio (A/B)</td>
</tr>
<tr>
<td>C_{max} (µg/mL)</td>
<td>657.12</td>
<td>598.25</td>
</tr>
<tr>
<td>AUC_{0-72} (µg.hr/mL)</td>
<td>4440.88</td>
<td>4034.52</td>
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The 90% confidence intervals for C_{max} and AUC_{0-72} were within the pre-defined limits acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Azithromycin 500 mg Tablets) and the reference formulation (Zithromax™ 500 mg Tablets).

Satisfactory justification is provided for a bio-waiver for the applicant’s lower strength tablets. As Azithromycin 250 mg and 500 mg Film-coated 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 for 500 mg formulation can be extrapolated to the other strength, i.e. 250 mg Film-coated Tablets.

**Pharmacodynamics**
No new data have been submitted and none are required for applications of this type.

**Clinical Efficacy**
No new data have been submitted and none are required.

**Clinical Safety**
No new data have been submitted and none are required.

**Expert Report**
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**
The SmPCs, PIL and labelling are medically satisfactory and consistent with those for the reference products.

**Marketing Authorisation Application (MAA) Forms**
The MAA forms are medically satisfactory.

**Conclusion**
There are no objections to the approval of these products from a clinical point of view.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Azithromycin 250 mg and 500 mg Film-coated 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of these type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Azithromycin 500 mg Tablets and the reference product, Zithromax™ 500 mg Tablets. As Azithromycin 250 mg and 500 mg Film-coated 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 for 500 mg formulation can be extrapolated to the other strength i.e. 250 mg Film-coated Tablets.

No new or unexpected safety concerns arose from these applications.

The SmPCs and PIL are satisfactory and consistent with those of the reference products, where appropriate. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with azithromycin anhydrous 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>
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