UK Public Assessment Report

Azithromycin 250 mg Capsules

PL 19156/0138

Jubilant Pharmaceuticals NV
This is a summary of the Public Assessment Report (PAR) for Azithromycin 250 mg Capsules (PL 19156/0138). It explains how Azithromycin 250 mg Capsules were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Azithromycin 250 mg Capsules.

For practical information about using Azithromycin 250 mg Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Azithromycin 250 mg Capsules and what are they used for?
Azithromycin 250 mg Capsules are a ‘generic medicine’. This means that they are similar to a ‘reference medicine’, already authorised in the European Union (EU) called Zithromax 250 mg Capsules.

Azithromycin 250 mg Capsules are used to treat bacterial infections caused by ‘micro-organisms’ such as bacteria. These infections include:
- chest, throat or nasal infections (such as 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

How do Azithromycin 250 mg Capsules work?
Azithromycin 250 mg Capsules contain the active substance azithromycin (as azithromycin dihydrate), which is an antibiotic. Azithromycin works by inhibiting proteins required for bacterial growth and function. Azithromycin belongs to a group of antibiotics called ‘macrolides’.

How are Azithromycin 250 mg Capsules used?
Azithromycin 250 mg Capsules should be swallowed whole with a glass of water.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

The usual dose for adults and young people with a bodyweight of 45 kg and above is 500 mg (2 capsules) taken together, once a day, for 3 days. The dose is different if there is inflammation of the tube that carries urine from the bladder (urethra) or inflammation of the tube where the womb joins the vagina (cervix). In this situation a doctor will advise that a single dose of 1000 mg (4 capsules) should be taken all together on one day only.

Azithromycin capsules should not be taken by children weighing less than 45 kg. Young people with a body weight of less than 45 kg should use other forms of this medicine, such as azithromycin suspension.

This medicine can only be obtained with a prescription.
How have Azithromycin 250 mg Capsules been studied?
Because Azithromycin 250 mg Capsules are a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Zithromax 250 mg Capsules. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side-effects of Azithromycin 250 mg Capsules?
Because Azithromycin 250 mg Capsules are a generic medicine, their benefits and possible side effects are taken as being the same as those of the reference medicine, Zithromax 250 mg Capsules.

For further information, please see the package leaflet.

Why are Azithromycin 250 mg Capsules approved?
It was concluded that, in accordance with EU requirements, Azithromycin 250 mg Capsules have been shown to have comparable quality and be bioequivalent to Zithromax 250 mg capsules, hard. Therefore, the view was that, as for Zithromax 250 mg capsules, hard, the benefits outweigh the identified risks and Azithromycin 250 mg Capsules can be approved for use.

What measures are being taken to ensure the safe and effective use of Azithromycin 250 mg Capsules?
A risk management plan has been developed to ensure that Azithromycin 250 mg Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Azithromycin 250 mg Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side-effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Azithromycin 250 mg Capsules
A marketing authorisation in the UK was granted to the marketing authorisation holder, Jubilant Pharmaceuticals NV, on 24 April 2015.

The full PAR for Azithromycin 250 mg Capsules follows this summary.

For more information about taking Azithromycin 250 mg Capsules, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in June 2015.
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I Introduction

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation (MA) to Jubilant Pharmaceuticals NV for the medicinal product Azithromycin 250 mg Capsules (PL 19156/0138) on 24 April 2015.

This product is a prescription-only medicine (POM), indicated in treatment of the following bacterial infections induced by micro-organisms susceptible to azithromycin:
- infections of the lower respiratory tract: acute exacerbation of chronic bronchitis (adequately diagnosed)
- mild to moderate community-acquired pneumonia infections of the upper respiratory tract
- sinusitis and pharyngitis/tonsillitis,
- acute otitis media
- infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulitis, erysipelas
- uncomplicated genital infections due to Chlamydia trachomatis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

This application was submitted as an abridged standard national application, according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product. The reference medicinal product, which has been authorised in accordance with Community provisions in force for not less than 10 years in the European Economic Area (EEA), is Zithromax 250 mg Capsules (PL 00057/0335); this product was authorised to Pfizer UK Limited in the UK on 04 April 1991.

Azithromycin is a macrolide antibiotic belonging to the azalide group. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis, by binding to the ribosomal 50S sub-unit and thus inhibiting the translocation of peptides.

No new non-clinical studies were conducted, which is acceptable given that this application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Since Azithromycin 250 mg Capsules are intended for generic substitution, this will not lead to an increased exposure to the environment. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

With the exception of a bioequivalence study, no new clinical data were provided with this application. One bioequivalence study was performed, which compared the pharmacokinetics of the applicant’s Azithromycin 250 mg Capsules with those of the reference product, Zithromax 250 mg Capsules, in healthy subjects under fasting conditions. It is stated by the applicant that the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP).

The RMS 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, assembly and batch release of this product.
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 of satisfactory inspection summary reports issued by the inspection services of the MHRA as certification that acceptable standards of GMP are in place at those non-Community sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and these are satisfactory.

The MHRA considered that the application could be approved and a licence was granted on 24 April 2015.
II Quality aspects

II.1 Introduction
This application was submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The applicant has specified Zithromax 250 mg Capsules (PL 00057/0335) as the EU reference medicinal product (MA Holder: Pfizer Limited).

Azithromycin 250 mg Capsules are formulated as hard white opaque gelatin capsules containing a white to off white granular powder. The gelatin capsules, size “0”, have a white body and cap, and are imprinted with “250” on the cap and body.

Each Azithromycin 250 mg Capsule contains azithromycin dihydrate, equivalent to 250 mg of azithromycin. The excipients present in each capsule are: microcrystalline cellulose (E460), pregelatinised maize starch, magnesium stearate (E470b), sodium laurilsulfate, gelatin and black ink (consisting of: shellac, propylene glycol, black iron oxide, potassium hydroxide).

The capsules are packed in white opaque polyvinyl chloride -aluminium (PVC -Al) blisters containing 2, 4 or 6 capsules.

II.2 Drug Substance
Azithromycin dihydrate

INN: azithromycin dihydrate
Chemical Name: \((2R,3S,4R,5R,6R,7R,8R,10R,11R,12S,13S,14R)-13-\{(2,6-Dideoxy-3-C-methyl-3-O-methyl-\alpha\text{-}L\text{-}ribo\text{-}hexopyranosyl)oxy\}-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-\{(3,4,6-trideoxy-3-(dimethylamino)-\beta\text{-}D\text{-}xylo\text{-}hexopyranosyl)oxy\}-1-oxa-6-azacyclopentadecan-15-one\)

Structure:

![Azithromycin dihydrate structure](image)

With \(x = 2\)

Molecular formula: \(C_{38}H_{72}N_2O_{12}\cdot 2H_2O\)
Molecular weight: 767
Appearance: white or almost white powder.
Solubility: practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride.

Azithromycin dihydrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, azithromycin dihydrate, are covered by an EDQM Certificate of Suitability.
II.3 Medicinal Product

Pharmaceutical development
The development of the product has been adequately described. The choice of excipients is justified and their functions explained.

Comparative dissolution profiles have been demonstrated between Azithromycin 250 mg Capsules and the UK reference medicinal product, Zithromax 250 mg Capsules (PL 00057/0335).

In order to show Azithromycin 250 mg Capsules are equivalent to the UK reference medicinal product, Zithromax 250 mg Capsules, with regard to bioavailability, a bioequivalence study was performed. This is discussed in Section IV – Clinical aspects.

All the excipients used in the manufacture of the proposed formulations, other than the black printing ink, comply with their respective European Pharmacopoeia monographs. The black printing ink complies with a satisfactory in-house specification.

Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients are sourced from animal or human origin, except for gelatin. The suppliers of the gelatin have provided certificates of suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the finished product, together with appropriate accounts of the manufacturing processes. Validation data was provided for the manufacturing processes.

Product Specification
The finished product specification is satisfactory. Satisfactory batch analyses for two pilot-scale batches of the finished product were performed. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from the studies support a shelf-life of 2 years, with the storage precaution ‘Store below 25 °C’ and ‘Store in the original package’.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.
III  Non-clinical aspects  
The pharmacodynamic, pharmacokinetic and toxicological properties of azithromycin dihydrate are well-known. As this active substance is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The non-clinical overview based on a literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person. The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is adequate.

Since Azithromycin 250 mg Capsules are intended for generic substitution, they will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

IV  Clinical aspects  
IV.1  Introduction  
With the exception of bioequivalence data, no new clinical data have been submitted and none are required for an application of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2  Pharmacokinetics  
In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

A randomized, open-label, balanced, two-treatment, two-sequence, two-period, single dose, two-way crossover bio-study was carried out on healthy adult human male subjects aged 18-45 and between 50 and 80 kg under fasting conditions to compare the bioavailability of the test product (Azithromycin 250 mg Capsules) with the reference product (Zithromax 250 mg Capsules).

Volunteers received the test or reference treatment after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post-dose. The two treatment periods were separated by a 31-day washout period.

The main pharmacokinetic results are presented below:
Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals (n = 45)

<table>
<thead>
<tr>
<th>SUMMARY RESULTS</th>
<th>Cmax [ng/mL]</th>
<th>AUC0-72 [ng*hr/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Untransformed Data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEST (T) Arithmetic Mean</td>
<td>414.2742</td>
<td>2342.9313</td>
</tr>
<tr>
<td>S.D.</td>
<td>182.07821</td>
<td>777.92540</td>
</tr>
<tr>
<td>C.V. (%)</td>
<td>43.95</td>
<td>33.20</td>
</tr>
<tr>
<td>N</td>
<td>45</td>
<td>45</td>
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<tr>
<td>REFERENCE (R) Arithmetic Mean</td>
<td>393.5019</td>
<td>2203.8592</td>
</tr>
<tr>
<td>S.D.</td>
<td>194.07706</td>
<td>759.50129</td>
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<tr>
<td>C.V. (%)</td>
<td>49.32</td>
<td>34.47</td>
</tr>
<tr>
<td>N</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td><strong>Log Transformed Data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSM(T)</td>
<td>5.0445</td>
<td>7.7016</td>
</tr>
<tr>
<td>LSM(R)</td>
<td>5.8622</td>
<td>7.6313</td>
</tr>
<tr>
<td>Geometric Mean(T)</td>
<td>381.6535</td>
<td>2211.9189</td>
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<tr>
<td>Geometric Mean(R)</td>
<td>351.4987</td>
<td>2061.7221</td>
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<tr>
<td>T/R Ratio (%)</td>
<td>108.58</td>
<td>107.29</td>
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<tr>
<td>90% C.I. (Calculated)</td>
<td>0.05 - 124.03</td>
<td>0.67 - 110.07</td>
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<tr>
<td>90% C.I. (BE Criteria)</td>
<td>80.00 - 125.00</td>
<td>80.00 - 125.00</td>
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<tr>
<td>Intersubject C.V. (%)</td>
<td>24.50</td>
<td>22.49</td>
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<tr>
<td>Intrasubject C.V. (%)</td>
<td>38.89</td>
<td>30.05</td>
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<tr>
<td>Power (%)</td>
<td>88.94</td>
<td>96.91</td>
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</table>

The 90% confidence intervals were within the acceptance criteria of 80.00%-125.00%. Based on these results, the proposed product, Azithromycin 250 mg Capsules, can be considered bioequivalent with the reference product Zithromax 250 mg Capsules.

**IV.3 Pharmacodynamics**

No new pharmacodynamics data are required for this application and none have been submitted.

**IV.4 Clinical efficacy**

No new clinical efficacy data are required for this application and none have been submitted.

**IV.5 Clinical safety**

With the exception of the bioequivalence study, no new data have been provided and none are required for this application. No serious adverse events were reported during the bioequivalence study. A total of 3 AEs occurred in one subject itself and were considered related to the study drugs.
IV.6 Risk Management Plan (RMP)
The marketing authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Azithromycin 250 mg Capsules.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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| Important identified risks| • Allergic reactions  
• Stevens-Johnson syndrome  
• Risk of superinfections  
• QT interval prolongation  
• Hepatic dysfunction  
• Precipitation or aggravation of myasthenia gravis  
• *Clostridium difficile* associated diarrhoea and pseudomembranous colitis  
• Use with ergot alkaloids  
• Use with oral anticoagulants  
• Use with P-gp substrates such as digoxin |
| Important potential risks | None |
| Missing information       | • Long term use  
• Use for the prevention or treatment of MAC (Mycobacterium Avium Complex) in children  
• Use in pregnancy  
• Use during breast feeding |

Planned risk minimisation activities
Risk minimization measures beyond the routine risk minimization activities, already listed in the SmPC and package leaflet, and the routine pharmacovigilance actions, are not considered necessary.

V.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Jubilant Azithromycin 250 mg and 500 mg Film-Coated Tablets, PL 19156/00556 & 0057, NL/H/1917/001-002. The bridging report submitted by the applicant is acceptable.
VI Overall conclusion, benefit/risk assessment and recommendation
The quality of this product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The application contains an adequate review of published clinical data. The test product, Azithromycin 250 mg Capsules, can be considered bioequivalent with the reference product, Zithromax 250 mg Capsules. The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), package leaflet and labelling are satisfactory, in line with current guidelines and consistent with the reference product. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and package leaflet for this product is available on the Medicines and Healthcare products Regulatory Agency website.

The currently approved labelling is listed below:
UKPAR Azithromycin 250 mg Capsules

PL 19156/0138

Keep out of the sight and reach of children.

AeroRinse Short spray

Each capsule, hard contains 250 mg azithromycin (as dihydrate).

Marketing authorisation holder:
Jubilant Pharmaceuticals nv
Access Business Park
Guldersporenpark 22 – Block C
9820 Molenbeke
Belgium

POM
PL 19156/0138
UKPAR Azithromycin 250 mg Capsules

PL 19156/0138

Keep out of the sight and reach of children.

Do not use.

Read the package leaflet before use.

Store below 25°C. Store in the original package.

Each capsule, hard contains 250 mg azithromycin (as dihydrate).

Marketing authorisation holder:
Jubilant Pharmaceuticals nv
Access Business Park
Gulierspoorpark 22 – Block C
9920 Merelbeke
Belgium

POM
PL 19156/0138
UKPAR Azithromycin 250 mg Capsules

Azithromycin capsules

Azithromycin 250 mg capsules

Each capsule hard contains 250 mg azithromycin (as dihydrate).

Marketing authorisation holder:
Jubilant Pharmaceuticals nv
Axxess Business Park
Guldenlopene Park 22 – Block C
9820 Merelbeke
Belgium

POM
PL 19156/0138
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Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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