Public Assessment Report

National Procedure

Azithromycin 250 mg capsules

(Azithromycin dihydrate)

Licence number: PL 33155/0078

Rivopharm UK Ltd
LAY SUMMARY

Azithromycin 250 mg capsules

Azithromycin dihydrate

This is a summary of the Public Assessment Report (PAR) for Azithromycin 250 mg capsules. 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?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Zithromax 250 Capsules (PL 00057/0355; Pfizer Limited)

Azithromycin 250 mg capsules are used to treat infections caused by certain bacteria and other micro-organisms, which 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 organisms called Chlamydia trachomatis and Neisseria gonorrhoea.

How do Azithromycin 250 mg capsules work?
Azithromycin 250 mg capsules contain the active ingredient azithromycin, which is one of a group of antibiotics called macrolides. This medicine works by killing the bacteria that causes infections.

How are Azithromycin 250 mg capsules used?
The pharmaceutical form of this medicine is a capsule and the route of administration is oral (by mouth). The capsule should be swallowed whole.

The recommended dose in adults and children over 7 stones (45 kg) is 500 mg (2 capsules) taken together, once a day, for 3 days.

For some diseases such as Chlamydia the recommended dose is 1 g (4 capsules) taken all together on one day only.

For gonorrhoea the recommended dose is 1 g or 2 g of azithromycin in combination with 250 or 500 mg of ceftriaxone.

Azithromycin capsules should not be taken by children weighing less than 45 kg.

The patient must tell a doctor if he/she has a kidney or liver problems as the patient’s doctor may need to alter the normal dose.
A doctor may sometimes prescribe a different dose to the recommended dose. The label on the pack will tell patients which dose they should take. If patients are still not sure, they should ask a doctor or pharmacist.

Patients must continue with the course even if they feel better. If an infection gets worse or the patient do not start to feel better within a few days or a new infection develops, the patient should go back to a doctor.

For further information on how Azithromycin 250 mg capsules are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription. The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

**What benefits of Azithromycin 250 mg capsules have been shown in studies?**
Because Azithromycin 250 mg capsules are a generic medicine, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicine. 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 and are bioequivalent to the reference medicine, their benefits and possible side effects are considered to be the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

**Why were Azithromycin 250 mg capsules approved?**
It was concluded that, in accordance with EU requirements, Azithromycin 250 mg capsules have been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it 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 (RMP) 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 SmPC and the package leaflet, 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/healthcare professionals will be monitored and reviewed continuously.

**Other information about Azithromycin 250 mg capsules**
A Marketing Authorisation for Azithromycin 250 mg capsules was granted in the UK on 07 March 2019.

The full PAR for Azithromycin 250 mg capsules follows this summary.
This summary was last updated in May 2019.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Azithromycin 250 mg capsules (PL 33155/0078) could be approved.

Azithromycin is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms:

- bronchitis
- community-acquired pneumonia
- sinusitis
- pharyngitis/tonsillitis (see section 4.4 of the SmPC regarding streptococcal infections)
- otitis media
- skin and soft tissue infections
- uncomplicated genital infections due to Chlamydia trachomatis and Neisseria gonorrhoeae.

Considerations should be given to official guidance regarding the appropriate use of antibacterial agents.

Azithromycin 250 mg capsules contain the active substance azithromycin, which is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicine. The reference medicinal product is Zithromax 250 mg Capsules (PL 00057/0335), which was granted a product licence in the UK to Pfizer Limited on 04 April 1991.

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

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of a reference product that has been in clinical use for over 10 years. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

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

A marketing authorisation was granted for this product on 07 March 2019.
II QUALITY ASPECTS

II.1 Introduction
This product consists of a hard gelatine capsules with an orange cap and a white body imprinted with “AZ 250”.

In addition to azithromycin dihydrate, this product also contains the following excipients:

**Capsule content**
- Sodium lauryl sulfate
- Sugar spheres
- Povidone

**Capsule shell**
- Titanium Dioxide (E171)
- Purified water
- Gelatine

**Printing ink**
- Shellac
- Dehydrate Alcohol (E1510)
- Isopropyl Alcohol
- Butyl Alcohol
- Propylene Glycol
- Strong Ammonia Solution
- Black Iron oxide (E172)
- Potassium Hydroxide
- Purified Water

The finished product is packaged in a white Alu/polyvinylchloride (PVC)-polyvinlylidenechloride (PVD) blisters of 2, 4 or 6 capsules.

Not all pack sizes may be marketed.

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.

II.2 ACTIVE SUBSTANCE
rINN: Azithromycin dihydrate
Chemical Name: \((2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-d-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one\)
Molecular Formula: \(C_{38}H_{72}N_{2}O_{12}, 2H_{2}O\)
Chemical Structure:
Molecular Weight: 749.0 g/mol
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 are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT
Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and reference products.

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

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatine have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

This product does not contain or consist of genetically modified organisms (GMO).

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

A satisfactory batch formula has been provided for the manufacture of the 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 specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.
Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, with the storage conditions “Store below 30°C” and “Store in the original container to protect from light” are acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of azithromycin dihydrate is well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of azithromycin dihydrate are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV.2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence study:

This study was a single center, randomised, single dose, laboratory-blinded, 4-period, 2-sequence, full replicate crossover study comparing the test product Azithromycin 250 mg capsules versus the reference product Zithromax 250 mg Capsules in subjects under fasted conditions.
Subjects were asked to fast for at least 10 hours prior to dosing. A single dose of the test or reference product was taken orally with approximately 240ml water.

Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 21 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intra subject C.V.(%)</th>
<th>Geometric LSMEANS</th>
<th>Ratio (%)</th>
<th>90% Confidence Limits (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Test (n=61)</td>
<td>Reference (n=61)</td>
<td></td>
</tr>
<tr>
<td>C\textsubscript{max}</td>
<td>35.9</td>
<td>222.14</td>
<td>217.19</td>
<td>102.28</td>
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<tr>
<td>AUC\textsubscript{0-72}</td>
<td>27.5</td>
<td>1550.05</td>
<td>1496.83</td>
<td>103.56</td>
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In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

**IV.3 Pharmacodynamics**
No new pharmacodynamic data have been submitted for this application and none were required.

**IV.4 Clinical efficacy**
No new efficacy data were submitted with this application and none were required.

**IV.5 Clinical safety**
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference product were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

**IV.6 Risk Management Plan (RMP)**
The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

**IV.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 PIL has been performed on the basis of a bridging report making reference to Zithromax 250 mg Capsules (PL 00057/0335; Pfizer Limited). The bridging report submitted by the Marketing Authorisation Holder (MAH) is acceptable.
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with azithromycin dihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) 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 PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.
Azithromycin capsules

For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 30°C.
Store in the original container to protect from light.

Azithromycin capsules

250 mg 4 Capsules

ORAL USE

Azithromycin capsules

250 mg 4 Capsules

MA Holder:
Rivopharm UK Ltd,
30th Floor, 40 Bank Street,
Canary Wharf
London, E14 5NR, UK

Generic, Article 10(1)
Azithromycin 250 mg capsules

For oral use. Read the package leaflet before use. Keep out of the sight and reach of children. Store below 30°C. Store in the original container to protect from light.

Azithromycin capsules

250 mg 6 Capsules

ORAL USE

MA Holder: Rivopharm UK Ltd, 30th Floor, 40 Bank Street, Canary Wharf, London, E14 5NR, UK

PL 33155/0078
Azithromycin 250 mg capsules
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 30°C.
Store in the original container to protect from light.

Azithromycin capsules
250 mg 6 Capsules

ORAL USE

Azithromycin capsules
250 mg 6 Capsules

MA Holder:
Rivopharm UK Ltd.
30th Floor, 40 Bank Street,
Canary Wharf
London, E14 5NR, UK

Generic, Article 10(1)
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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

<table>
<thead>
<tr>
<th>Application type</th>
<th>Scope</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Outcome</th>
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