Azithromycin 500mg Powder for Solution for Infusion

PL 10622/0306

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 16
Steps taken after authorisation Page 17
Summary of Product Characteristics Page 18
Product Information Leaflet Page 29
Labelling Page 35
Azithromycin 500mg Powder for Solution for Infusion

PL 10622/0306

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted PLIVA Pharma Limited a Marketing Authorisation (licence) for the medicinal product Azithromycin 500mg Powder for Solution for Infusion (PL 10622/0306) on 27 September 2011. This is a prescription-only medicine (POM).

Azithromycin is one of a group of antibiotics called macrolides. This medicine is used to treat the following serious infections when these require admission to hospital and when the infection is caused by micro-organisms that are susceptible to azithromycin:

- Pneumonia acquired outside of hospital
- Infection of the internal female sex organs (Pelvic Inflammatory Disease)

This medicinal product is used when you require treatment by intravenous infusion (a ‘drip’). The medicine is ready to be reconstituted (dissolved in liquid) to be given by infusion.

Azithromycin 500mg Powder for Solution for Infusion was considered to be a generic version of a European reference product, Azitromax 500mg Powder for Solution for Infusion (MA number 16698, Pfizer AB, Sweden), based on the data submitted by PLIVA Pharma Limited.

No new or unexpected safety concerns arose from this application. It was judged that the benefits of Azithromycin 500mg Powder for Solution for Infusion outweigh the risks; hence a Marketing Authorisation has been granted.
Azithromycin 500mg Powder for Solution for Infusion

PL 10622/0306

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 6
Non-clinical assessment Page 10
Clinical assessment Page 11
Overall conclusion and risk benefit assessment Page 15
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted PLIVA Pharma Limited a Marketing Authorisation for the medicinal product Azithromycin 500mg Powder for Solution for Infusion (PL 10622/0306) on 27 September 2011. The product is a prescription-only medicine (POM).

This is a generic application for Azithromycin 500 mg Powder for Solution for Infusion, submitted according to Article 10.1, 3rd Paragraph of Directive 2001/83/EC, as amended. The application refers to a European reference medicinal product, Azitromax 500mg Powder for Solution for Infusion, which was authorised to Pfizer AB in Sweden on 12 December 2003 (MA number 16698). The European reference medicinal product has been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired. Azithromycin (Zithromax, Pfizer) oral products have been continuously marketed in the UK since 1991. An intravenous preparation of azithromycin has not been authorised in the UK but this route has been licensed in Sweden (2003), Denmark (2003), Canada (1999) and the USA (1998). The UK reference product is Azithromax 500 mg Tablets (PL 00057/0391), authorised to Pfizer Limited on 17 September 1996.

The application was referred to the Commission on Human Medicines (CHM) who met in October 2008 for consideration whether the safety, quality and efficacy of the product was demonstrated. Following consideration of the applicant’s responses and further data that were submitted, the approval of the Marketing Authorisation was recommended.

Azithromycin 500mg Powder for Solution for Infusion is indicated for the treatment of the following infections in adult patients who require intravenous therapy (see sections 4.4 and 5.1):

- Community-acquired pneumonia
- Pelvic Inflammatory Disease

Consideration should be given to official guidance regarding the appropriate use of antibacterials.

Azithromycin is a macrolide antibiotic (ATC classification: J01FA10) belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0. 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.

Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.
Complete cross-resistance exists among *Streptococcus pneumoniae*, beta-haemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

The medicinal product is supplied in a lyophilised form in a 14 ml vial containing 500 mg azithromycin, as monohydrate. After reconstitution with sterile water for injection, the product contains 100mg/ml. The reconstituted solution requires further dilution to a final infusion concentration of 1 or 2 mg/ml prior to administration.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that this is a generic application cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

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 this product.

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 detailed Risk Management Plan (RMP). As the application is for a generic version of an 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 product has been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the product.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Azithromycin monohydrate

Nomenclature:

INN: Azithromycin

Chemical names:

i) (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

ii) 1-Oxa-6-azacyclopentadecan-15-one, 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]-, [2R (2R*, 3S*, 4R*, 5R*, 8R*, 10R*, 11R*, 12S*, 13S*, 14R*)]

iii) 9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A

Structure:

![Structure of Azithromycin Monohydrate](image)

Molecular formula: C_{38}H_{72}N_{2}O_{12}.H_{2}O

Molecular weight: 767.0 g/mol (749 g/mol for the anhydrous substance)

CAS No: 121479-24-4 (Azithromycin monohydrate)

Physical form: A white to almost white powder

Solubility: Freely soluble in acetone, acetonitrile, chloroform, dimethylformamide, dimethylsulfoxide, alcohol, ethyl acetate, isopropanol and methanol; poorly soluble in water. The solubility of azithromycin monohydrate decreases with increasing pH.

The active substance, azithromycin monohydrate, is the subject of a European Pharmacopeia (Ph Eur.) and USP 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 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 reference standards used by the active substance manufacturer 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 for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been applied.

**MEDICINAL PRODUCT**

**Description & Composition**

Azithromycin 500 mg Powder for Solution for Infusion is presented as a white to almost white powder for solution for infusion. The medicinal product is supplied in a lyophilised form in a 14 ml vial containing 500 mg azithromycin, as monohydrate. After reconstitution with sterile water for injection, the product contains 100mg/ml. The reconstituted solution requires further dilution to a final infusion concentration of 1 or 2 mg/ml prior to administration.

Other ingredients consist of pharmaceutical excipients, namely citric acid monohydrate and sodium hydroxide (for pH adjustment). Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

**Physiochemical properties**

A comparison of the physiochemical properties of the test and reference products has been provided. Comparative impurity profiles were provided for batches of test and reference products. All impurities were within the specification limits.
Pharmaceutical development
Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The aim was to develop a stable, generic formulation of the European reference product, Azitromax 500mg Powder for Solution for Infusion (Pfizer AB, Sweden).

The active substance in the proposed product is a monohydrate in contrast to a dihydrate in the reference product. Since both products are powders to be dissolved in water for infusion, the hydrate form is irrelevant and is not expected to affect the in vivo behaviour of the active substance.

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrate consistency of the manufacturing process.

Finished product specification
The 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
Azithromycin 500 mg Powder for Solution for Infusion is supplied in a lyophilised form in a clear, type I 14 ml glass vial, with a bromobutyl rubber stopper and aluminium/polypropylene flip off seal. The vial is packaged, with the package leaflet, into a cardboard outer carton.

Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. The vials satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations.

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 a shelf-life of 2 years. This medicinal product does not require any special storage conditions.

Chemical and physical in-use stability for reconstituted concentrate has been demonstrated for 24 hours at 25°C or 7 days in refrigerator at 2-8°C.
After reconstitution and dilution, the mixed solution is chemically and physically stable for 24 hours at 30°C or 7 days in refrigerator (at 2-8°C). However, from a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.

For full details of shelf-life and storage conditions for the medicinal product and reconstituted medicinal product, refer to section 6.3 of the SmPC. This medicinal product must not be mixed or co-administered with other medicinal products except those mentioned in section 6.6 of the SmPC. Please refer to Section 6.6 of the SmPC for information on proper handling, preparation of infusion, dilution and disposal for the product.

**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 Summary of Product Characteristics (SmPC), and Patient Information Leaflet (PIL) and labelling texts are satisfactory. The labelling texts fulfil the statutory requirements for Braille. The MAH has submitted text versions only and has committed to submitting mock-up livery and the supporting PIL user test to the MHRA for approval before packs are marketed.

**Conclusion**

The proposed product has been shown to be a generic version of the reference product, Azitromax 500mg Powder for Solution for Infusion (Pfizer AB, Sweden), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the EU for over 10 years.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. There are no objections to approval of Azithromycin 500 mg Powder for Solution for Infusion from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

This generic application, submitted under Article 10.1, 3rd Paragraph of Directive 2001/83/EC, as amended, is for Azithromycin 500 mg Powder for Solution for Infusion, claiming to be a generic medicinal version of the European reference medicinal product, Azitromax 500mg Powder for Solution for Infusion (Pfizer AB).

No new non-clinical data have been supplied with this application and none are required for applications of this type.

A non-clinical overview has been written by a suitably qualified person and is satisfactory. The overview, dated October 2006, cites 34 references from the published literature dated up to year 2001. The CV of the expert has been supplied.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

There are no objections to approval of this product from a non-clinical point of view.
CLINICAL ASSESSMENT

CLINICAL BACKGROUND

Azithromycin is a semi-synthetic macrolide antibiotic with a broader spectrum of activity than clarithromycin or erythromycin. Azithromycin is better absorbed than other macrolides when taken orally. Oral azithromycin may be given as single-dose therapy in some situations and is more likely to be effective in cases where compliance is a problem. The relative lack of drug interactions makes azithromycin an attractive option in patients who are already taking many drugs, e.g. patients on HIV therapy.

The applicant seeks to obtain a licence for an intravenous formulation of azithromycin. Intravenous azithromycin is not available in the UK. The applicant refers to the Swedish product (produced by Pfizer) as the European reference product. The intravenous product is intended for the treatment of community-acquired pneumonia (CAP) and pelvic inflammatory disease (PID) in patients who require initial intravenous therapy. The recommended dosing regimens are for CAP – 500 mg azithromycin i.v. daily for at least two days followed by 500 mg oral azithromycin daily for a total of up to 10 days therapy and for PID – 500 mg azithromycin i.v. daily for one or two days followed by 250 mg oral azithromycin daily for a total of up to 7 days therapy. Approval for the use of azithromycin i.v. in these indications has already been gained in the United States (1998) and Canada (1999) with the same dosing regimens.

Community acquired pneumonia

Pneumonia is an inflammation of the lower air passages and air sacs of the lungs resulting from infection of the parenchyma of the lungs. It is very common and most of the infections are in elderly patients. The mortality rate is up to 50%.

Most community-acquired pneumonias are bacterial and the predominant pathogen is Streptococcus pneumoniae. Up to 13% of community-acquired pneumonias are viral in origin. Influenza A and B viruses are the predominant viral pathogens. Viral pneumonia is more common in the autumn and winter.

It is not possible to distinguish the causative organisms of pneumonia other than by microbiology as no pathogen leads to a clinical, laboratory or radiological pattern sufficiently characteristic to be the basis of a confident diagnosis, but clinical symptoms and epidemiological features may provide clues to the aetiology as some differences in presentation do occur.

It is helpful to distinguish between typical and atypical pathogens in pneumonia. The distinction may only be determined by microbiology, not by clinical signs and symptoms. Atypical pathogens are less common in patients aged 75 years and over.

Early antibiotic administration (within eight hours of hospital arrival) improves outcome. The choice of antibiotic, route of administration, and dose depend on the severity of the disease, probable pathogens and local resistance patterns. The British Society for Antimicrobial Chemotherapy recommends that if the patient is severely ill, unconscious or vomiting, intravenous therapy will be required.
The British Society for Antimicrobial Chemotherapy (2008) recommends that the agent chosen should always cover the most likely pathogen: *Streptococcus pneumoniae*. It should also cover *Haemophilus influenzae* (still the second most common pathogen causing pneumonia).

Atypical pathogens such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* are less common but are more frequent in patients <75 years. *Mycoplasma pneumoniae* infection tends to be more frequent in winter, in addition to its pattern of four-yearly epidemics. *Staphylococcus aureus* is an uncommon cause of community-acquired pneumonia but should be considered during influenza epidemics.

A cluster of atypical infections may suggest Legionnaires’ disease (although it is often not possible to distinguish atypical pathogens clinically and Legionnaires’ disease is often diagnosed in retrospect).

The antibiotics chosen should be able to penetrate into alveolar tissue and fluid, and if the suspected pathogen is intracellular, such as Legionella or *Mycoplasma* spp., then the antibiotics chosen should also be capable of penetration into cells.

Treatment duration depends on the causative organism and clinical response.

Patients with severe pneumonia are diagnosed by having two or more of the core features of the CURB score (based on confusion, urea concentration, respiratory rate, blood pressure). The British Thoracic Society (2004) recommends that patients with a CURB score of 2 or more should be managed in hospital because they are at high risk of death.

The British Society for Antimicrobial Chemotherapy (2008) recommends the following for the treatment of severe pneumonia of unknown aetiology: combination treatment with a macrolide plus an injectable cephalosporin (exact agents to be determined by local policy).

**Pelvic inflammatory disease**

According to the Royal College of Obstetricians and Gynaecologists (2003), pelvic inflammatory disease (PID) is a common cause of morbidity and accounts for 1 in 60 GP consultations by women under the age of 45. Delays of only a few days in receiving appropriate treatment markedly increase the risk of sequelae, which include infertility, ectopic pregnancy and chronic pelvic pain.

PID is usually the result of infection ascending from the endocervix causing endometritis, salpingitis, parametritis, oophoritis, tubo-ovarian abscess and/or pelvic peritonitis. While sexually transmitted infections such as *Chlamydia trachomatis* and *Messeria gonorrhoeae* have been identified as causative agents, *Mycoplasma genitalium*, anaerobes and other organisms may also be implicated.

The Royal College of Obstetricians and Gynaecologists acknowledges that there are marked variations in the antimicrobial regimens used in the treatment of PID presumably reflecting uncertainty in the optimal treatment schedule. Most cases are treated as an outpatient with appropriate oral antibiotic therapy. The NHS Clinical
Knowledge Summaries (formerly PRODIGY) (2008) advises treatment with broad-spectrum antibiotics to cover *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and anaerobic infection.

The Royal College of Obstetricians and Gynaecologists (2003) advises that admission to hospital would be appropriate in the following circumstances:

- surgical emergency cannot be excluded
- clinically severe disease
- tubo-ovarian abscess
- pregnancy (avoid macrolides)
- lack of response to oral therapy
- intolerance to oral therapy.

And that, in more severe cases, inpatient antibiotic treatment should be based on intravenous therapy, to be continued until 24 hours after clinical improvement and then followed by oral therapy. The exact agents used should be based on local knowledge / expertise.

**INDICATIONS**

Azithromycin 500mg Powder for Solution for Infusion is indicated for the treatment of the following infections in adult patients who require intravenous therapy (see sections 4.4 and 5.1):

- Community-acquired pneumonia
- Pelvic Inflammatory Disease

Consideration should be given to official guidance regarding the appropriate use of antibacterials.

The indications are consistent with those of the European reference medicinal product and are satisfactory.

**POSOLOGY AND METHOD OF ADMINISTRATION**

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the European reference medicinal product and is satisfactory.

**TOXICOLOGY**

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

**CLINICAL PHARMACOLOGY**

The clinical pharmacology of azithromycin is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.
EFFICACY

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of azithromycin is well-established from its extensive use in clinical practice.

Azithromycin 500mg Powder for Solution for Infusion is to be administered as an intravenous solution and contains the same active substance, in the same concentration, as the European reference medicinal product, Azitromax 500mg Powder for Solution for Infusion (Pfizer AB). Thus, in accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), Section 5.1.6 Parenteral solutions, the applicant is not required to submit a bioequivalence study.

SAFETY

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

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product and is acceptable.

Patient Information Leaflet (PIL)

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

Labelling

The labelling text is satisfactory.

Clinical overview

A clinical overview has been written by a suitably qualified person and is satisfactory. The overview, dated October 2006, cites 37 references from the published literature dated up to year 2005. The CV of the expert has been supplied.

CONCLUSION

Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Azithromycin 500mg Powder for Solution for Infusion 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 this type.

CLINICAL
No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview.

The applicant’s Azithromycin 500mg Powder for Solution for Infusion has been demonstrated to be a generic version of the European reference medicinal product, Azitromax 500mg Powder for Solution for Infusion (Pfizer AB).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is consistent with that for the European reference medicinal product and is satisfactory.

The PIL text is in line with the SmPC and is satisfactory.

The approved labelling text is satisfactory and fulfils 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 and the supporting PIL user test to the MHRA for approval before packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Azithromycin 500mg Powder for Solution for Infusion and the reference medicinal product, Azitromax 500mg Powder for Solution for Infusion (Pfizer AB), are interchangeable. Extensive clinical experience with azithromycin is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Azithromycin 500mg Powder for Solution for Infusion

PL 10622/0306

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application on 13th December 2006.

2. Following standard checks and communication with the applicant the MHRA considered the application valid on 14th February 2007.

3. Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 28th February 2007, 28th August 2007, 9th October 2007, 1st February 2008 and 18th July 2011; and further information relating to the quality dossier in October 2008, March 2011 and April 2011.

4. The applicant responded to the MHRA’s requests, providing further information for the clinical sections on 28th August 2007, 9th October 2007, 28th December 2007, 6th August 2008 and 16th September 2011; and further information for the quality sections in September 2010 and June 2011.

5. The MHRA sought advice from the Commission on Human Medicines (CHM) with regards to issues raised during assessment. The CHM met in October 2008 and issued their advice. Following consideration of the applicant’s responses and further data that were submitted, the approval of the Marketing Authorisation was recommended.

6. The application was determined on 27th September 2011.
Azithromycin 500mg Powder for Solution for Infusion

PL 10622/0306

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Azithromycin 500mg Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains 500 mg azithromycin (as monohydrate) and gives a concentrate of 100 mg/ml after reconstitution. The concentrate should be further diluted to 1 mg/ml or 2 mg/ml.

Excipient: 114 mg of sodium (as hydroxide) per vial.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for infusion.
White to almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Azithromycin 500mg Powder for Solution for Infusion is indicated for the treatment of the following infections in adult patients who require intravenous therapy (see sections 4.4 and 5.1):

Community-acquired pneumonia
Pelvic Inflammatory Disease

Consideration should be given to official guidance regarding the appropriate use of antibacterials.

4.2 Posology and method of administration
Community-acquired pneumonia: 500 mg as intravenous infusion once daily for at least two days, followed by oral azithromycin 500 mg as a single daily dose to complete a 7-10 day treatment in total.

Pelvic Inflammatory Disease including urogenital infections such as endometritis and salpingitis: 500 mg as intravenous infusion once daily, followed by oral azithromycin 250 mg as a single daily dose to complete a 7 day treatment in total.

Appropriate clinical guidelines should be followed regarding timing of change from intravenous to oral therapy (see sections 4.4 and 5.1)

Elderly
No dose adjustment is necessary for elderly patients.

Patients with renal impairment
In patients with mild renal impairment (creatinine clearance >40 ml/min), the same dosage as in patients with normal renal function may be used. Caution should be exercised when azithromycin is administered to patients with severe renal impairment (creatinine clearance < 10ml/min) (see section 4.4).

Patients with hepatic impairment
In patients with mild to moderate hepatic impairment, the same dosage as in patients with normal hepatic function may be used (see section 4.4).
Children
The safety and effectiveness of intravenous azithromycin for treatment of infections in children and adolescents under 16 years have not been established.

Administration
This medicinal product is administered as an intravenous infusion over 3 hours with a concentration of 1 mg/ml, or over 1 hour with a concentration of 2 mg/ml. Higher concentrations should be avoided as all tested subjects receiving infusion concentrations higher than 2 mg/ml experienced local reactions at the infusion site. The azithromycin infusion time should not be shorter than 60 minutes. Azithromycin should not be given as a bolus or intramuscular injection.

For preparation of infusion concentrate and prepared solution, please see section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications
Hypersensitivity to azithromycin, to any macrolide, or to any of the excipients.

Azithromycin should not be co-administered with ergot derivatives because of the theoretical possibility of ergotism.

4.4 Special warnings and precautions for use
An antimicrobial agent with anaerobic activity should be administered in combination with azithromycin if anaerobic microorganisms are suspected of contributing to the infection.

The safety of intravenous azithromycin has not been assessed beyond the timeframes described in the clinical trials of use in patients with community-acquired pneumonia and pelvic inflammatory disease (see section 5.1).

Rare serious allergic reactions (rarely fatal) including, angioneurotic oedema with anaphylaxis has been reported. Some of these reactions have caused recurrent symptoms and have required longer observation and treatment.

In patients with severe renal impairment (creatinine clearance<10ml/min), a 33% increase in systemic exposure to azithromycin has been observed.

Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see Section 4.8 Undesirable effects). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

Prolonged cardiac repolarization and QT interval which involve a risk of developing cardiac arrhythmia and torsades de pointes has been reported during treatment with other macrolides. A similar effect with azithromycin cannot be excluded. Because of this, azithromycin should be used with caution when there is a risk for increased QT interval as in non-corrected hypokalaemia and/or hypomagnesaemia, circumstances leading to prolonged cardiac repolarization, a case history of ventricular arrhythmias or bradycardia (<50bpm) (see section 4.8).

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Strains of C. difficile producing hypertoxin A and B contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity
and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. Therefore, CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific treatment for C. difficile should be considered.

As with any antibacterial agent, there is a possibility that superinfections could occur (e.g. fungal infections).

This medicinal product contains 5mmol sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be observed when azithromycin is given to patients treated with other drugs that may prolong the QT-interval (see section 4.4).

Effects of other drugs on azithromycin:
Nelfinavir: Co-administration of 1200 mg azithromycin and steady state nelfinavir (750 mg 3 times daily) resulted in a mean decrease of AUC of 16% for nelfinavir, an increase of AUC of azithromycin of 113%, and an increase of C_{max} with 136%. Dose adjustment is not necessary but enhanced attention on known side effects of azithromycin should be considered.

Antacids: Concomitant intake of oral azithromycin and antacids decrease the maximum serum concentration of azithromycin, but the total bioavailability is not affected.

Patients treated with both oral azithromycin and antacids should not take the drugs at the same occasion. Administration of oral antacid is not considered to have an effect on the disposition of intravenous azithromycin.

Rifabutin: Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed at concomitant treatment with azithromycin and rifabutin. Although neutropenia has been reported during treatment with rifabutin, a causal relationship to concomitant combination treatment with azithromycin has not been established (see section 4.8).

Effects of azithromycin on other drugs:
Zidovudine: 1000 mg single doses and 600 mg or 1200 mg multiple doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of the active phosphorylated zidovudine metabolites in peripheral blood mononuclear cells. The clinical significance of these findings is unclear.

Digoxin: In some patients certain macrolide antibiotics have been reported to impair the microbiological metabolism of digoxin in the intestine. In patients receiving concomitant treatment with azithromycin and digoxin, the possible risk of increased digoxin levels must be considered.

Even though azithromycin does not seem to inhibit the enzyme Cytochrome P450 3A4 (CYP3A4), a possible inhibition of this enzyme in each patient cannot be excluded. Consequently, caution is requested when given in combination with ciclosporin, ergot alkaloids, pimozide, astemizole, and other drugs with a narrow therapeutic window with a metabolism catalyzed by CYP3A4.

Ciclosporin: If coadministration is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Coumarin-Type Oral Anticoagulants: consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.
Ergot derivatives: Because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered.

Theophylline: Theophylline levels may be increased in patients taking azithromycin.

Absence of clinical significant interactions:
Concomitant use of azithromycin and the following drugs did not show any pharmacokinetic or pharmacodynamic interaction of clinical relevance: carbamazepine, cimetidine, didanosine, efavirenz, fluconazole, indinavir, methylprednisolone, midazolam, triazolam and trimethoprim/sulfamethoxazole.

4.6 Fertility, Pregnancy and lactation

Pregnancy: Whilst animal studies have shown no evidence of teratogenic effects, there is no experience of azithromycin in human pregnancy. Since animal studies are not always predictive of human response this medicinal product should not be administered to women who are pregnant unless there are compelling clinical reasons.

Lactation: There are no data on the secretion of azithromycin in breast milk. Breast feeding should therefore be discontinued during therapy.

As safety in use at pregnancy and lactation is unestablished, azithromycin should only be used where adequate alternatives are not available.

4.7 Effects on ability to drive and use machines

Even though somnolence has been reported as a less common adverse event in clinical studies at intravenous administration, there are no indications that azithromycin has produced any effect on the ability to drive or use machines.

4.8 Undesirable effects

When administering azithromycin, intravenously or orally, for treatment of community acquired pneumonia, diarrhoea/loose stools, nausea, stomach-ache, and vomiting were the most commonly reported undesirable effects. Local inflammation/pain at the infusion site has been reported with intravenous administration of azithromycin. The frequency and severity of these reactions were the same when 500 mg azithromycin was given over 1 hour (2 mg/ml as 250 ml infusion) or over 3 hours (1 mg/ml as 500 ml infusion).

At intravenous and oral administration of azithromycin for treatment of pelvic inflammatory disease in adult women, diarrhea, nausea, vaginitis, stomach-ache, anorexia, rashes and itching were the most commonly reported undesirable effects. At concomitant administration of azithromycin and metronidazole, a larger part of the women experienced undesirable effects such as nausea, stomach-ache, vomiting, irritation at the infusion site, stomatitis, dizziness or dyspnoea.

The following undesirable effects have been reported at the use of all of the dosage forms of azithromycin whereas the frequency is based on the reporting using an intravenous dosage schedule (1-2 days of intravenous administration followed by oral azithromycin in totally 7-10 days treatment).

| Common | General: Local pain and inflammation at infusion site |
| (>
1/100, <1/10) | GI: Abdominal discomfort (pain/cramps), diarrhoea (seldom resulting in dehydration), nausea, dyspepsia, vomiting. |
| | Liver: increased liver function test values (AST, ALT, alkaline phosphatases, bilirubin) |

| Uncommon | CNS: Headache, somnolence, taste perversion |
| (>1/1000, 1/100) | GI: Flatulence |
| | Skin and subcutaneous tissue: Rash, pruritus, oedema |
| | Other: Moniliasis (Candidiasis) |
Rare

General: Asthenia, fatigue, discomfort, anorexia

Blood: Neutropenia, thrombocytopenia.

CNS: Dizziness, paraesthesia, convulsions, hyperactivity, syncope

Circulation: Arrhythmias with associated ventricular tachycardia, palpitations, QT prolongation, torsades de pointes*. Hypotension.

Immunol: Anaphylaxis, anaphylactic shock.

GI: Constipation, loose stools, pancreatitis, pseudomembranous colitis, discoloration of tongue

Skin and subcutaneous tissue: Urticaria, allergic reactions, angioneurotic oedema, photosensitivity, serious skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Liver: Hepatitis and cholestatic jaundice, hepatic necrosis and hepatic failure (seldom fatal)

Psych: Nervousness, aggressiveness, agitation, anxiety

Musculoskeletal, connective tissue and bone disorders: Arthralgia

Urogenital: Interstitial nephritis and acute renal failure.

Ear: Impaired hearing loss of hearing included, deafness. Tinnitus, vertigo

Eyes: Visual disorders

Other: Vaginitis

* Palpitations and arrhythmias including ventricular tachycardia (as seen with treatment with other macrolides) have been reported. There have been rare reports of QT prolongation and torsades de pointes. A causal relation between azithromycin and these effects have not been possible to exclude (see section 4.4 Special Warnings and Special Precautions for Use).

Impaired hearing, including deafness and/or tinnitus has been reported in clinical trials at prolonged use with high doses. In those events possible to follow up, the impaired hearing has in the majority of cases been reversible.

Occasional cases of hepatic necrosis and hepatic failure, which in rare cases were fatal, have been reported. However, a casual relationship has not been established.

Laboratory values: abnormal liver values have been reported. The incidence of clinical significant increased liver function values was 4-5% in clinical studies where patients with community acquired pneumonia were treated with an intravenous infusion of azithromycin followed by oral treatment.

A mild, transient decrease in the number of neutrophilic blood cells has been observed in a low number of patients, but the causality with azithromycin is unclear.

Fungal growth in the oral cavity and genitals may occur.

4.9 Overdose

There is limited experience of overdosage. Typical symptoms: nausea, vomiting, diarrhoea, abdominal pain. Hepatic dysfunction and reversible hearing impairment may also occur.

Treatment: Symptomatic treatment and supportive measures as required.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides

ATC classification: J01FA10

Mode of action:

Azithromycin 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 chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0. 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.

Mechanism of resistance:

Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Complete cross resistance exists among *Streptococcus pneumoniae*, beta-haemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

 breakpoints:

The minimum inhibitory concentration (MIC) breakpoints separating susceptible and resistant organisms have been defined as follows (EUCAST 2008):

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Species-related breakpoints (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Streptococcus A,B,C,G</td>
<td>≤ 0.25</td>
</tr>
<tr>
<td><em>S. pneumonia</em></td>
<td>≤ 0.25</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>≤ 0.12</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>≤ 0.5</td>
</tr>
<tr>
<td><em>N. gonorrhoea</em></td>
<td>&gt; 0.25</td>
</tr>
</tbody>
</table>

1 Erythromycin can be used to determine the susceptibility of the listed bacteria to the other macrolides (azithromycin, clarithromycin and roxithromycin). Macrolides administered intravenously are active against *Legionella pneumophila* (erythromycin MIC ≤ 1 mg/L for wild type isolates). Macrolides have been used in the treatment of infections with *Campylobacter jejuni* (erythromycin MIC ≤ 4 mg/L for wild type isolates). Azithromycin has been used in the treatment of infections with *S. typhi* (MIC ≤ 16 mg/L for wild type isolates) and Shigella spp.

2 The correlation between *H. influenzae* macrolide MICs and clinical outcome is weak. Therefore, breakpoints for macrolides and related antibiotics were set to categorise wild type *H. influenzae* as intermediate.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.
Table: Antibacterial spectrum of Azithromycin

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic Gram-positive microorganisms</strong></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> methicillin-susceptible</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> penicillin-susceptible</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em> (Group A)</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative microorganisms</strong></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td><em>Haemophilus parainfluenzae</em></td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
</tr>
<tr>
<td><strong>Anaerobic microorganisms</strong></td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
</tr>
<tr>
<td>Fusobacterium spp.</td>
</tr>
<tr>
<td>Prevotella spp.</td>
</tr>
<tr>
<td>Porphyromonas spp.</td>
</tr>
<tr>
<td><strong>Other microorganisms</strong></td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
</tr>
<tr>
<td><em>Chlamydia pneumonia</em></td>
</tr>
<tr>
<td><em>Chlamydia psittaci</em></td>
</tr>
<tr>
<td><em>Mycoplasma pneumonia</em></td>
</tr>
<tr>
<td><em>Mycoplasma hominis</em></td>
</tr>
<tr>
<td><strong>Species for which acquired resistance may be a problem</strong></td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive microorganisms</strong></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> penicillin-intermediate and penicillin-resistant</td>
</tr>
<tr>
<td><strong>Inherently resistant organisms</strong></td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive microorganisms</strong></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
</tr>
<tr>
<td>Staphylococci MRSA, MRSE *</td>
</tr>
<tr>
<td><strong>Anaerobic microorganisms</strong></td>
</tr>
<tr>
<td>Bacteroides fragilis group</td>
</tr>
</tbody>
</table>
Methicillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

**Treatment of community acquired pneumonia**

In an open-label, non-comparative study, the patients were given azithromycin as an IV infusion (for 2-5 days) followed by oral azithromycin (to complete 7-10 days' therapy) for the treatment of community-acquired pneumonia. The clinical success rate (cure and improved) among evaluable patients was 88% 10-14 days post-therapy and 86% after 4-6 weeks.

In an open, randomised, comparative study, no statistically difference in outcome was observed between azithromycin (intravenous infusion followed by oral treatment) and cefuroxime (intravenous infusion followed by oral treatment, and erythromycin when needed) for the treatment of community acquired pneumonia.

In an open non-comparative study, patients with community acquired pneumonia diagnosed as positive for Legionella pneumophila (serogroup 1) were treated with azithromycin intravenous infusion followed by oral treatment. After 10-14 days, 16 of 17 evaluable patients were classified as clinically cured and after 4-6 weeks, 20 of 20 evaluable patients were classified as clinically cured.

**Treatment of Pelvic Inflammatory Disease including, urogenital infections as endometritis and salpingitis.**

The results from an open-label study indicate that three different treatment regimens (azithromycin versus azithromycin/metronidazol versus doxycycline, metronidazole, cefoxitin and probenicid, respectively) were comparable regarding efficacy and safety in patients with acute pelvic inflammatory disease.

In open-label, comparative study of patients with acute pelvic inflammation (salpingitis, endometritis etc.), patients received treatment with either azithromycin orally/intravenous infusion, or azithromycin intravenous infusion plus intravenous/oral metronidazole, or oral doxycycline plus intravenous/oral co-amoxiclav. These treatment regimens were also comparable regarding efficacy and safety. Data from these studies showed an overall clinical success rate cured and improved of ≥ 97% in all treatment groups at the end of treatment, with ≥ 96% of the pathogens eradicated. At follow-up ≥ 90% of the pathogens were eradicated.

Patients in the trials on pelvic inflammatory disease received 500mg azithromycin per day as an IV infusion (for a maximum of 3 days) followed by 250mg oral azithromycin per day for a total treatment period of up to 7 days.

**5.2 Pharmacokinetic properties**

In patients hospitalized with community-acquired pneumonia receiving a daily one-hour intravenous infusions of 500 mg azithromycin at a concentration of 2 mg/ml, the mean C\textsubscript{max} ± SD achieved was 3.63 ± 1.60 µg/ml while the lowest concentration (24 hour) was 0.2 ± 0.15 µg/ml, and AUC\textsubscript{24} was 9.6 ± 4.80 µg⋅h/ml.

In normal volunteers receiving a 3 hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/ml, the mean C\textsubscript{max}, lowest concentration (24 hour) and AUC\textsubscript{24} were 1.14 ± 0.14 µg/ml, 0.18 ± 0.02 µg/ml, and 8.03 µg⋅h/ml, respectively.

Following oral administration, considerably higher levels of azithromycin have been shown in different tissues e.g. lung, tonsils, or prostate, where the concentration of azithromycin is up to 50 times higher than in plasma. High concentrations of azithromycin have been registered in gynecological tissue 96 hours after 500 mg of orally azithromycin as a single dose.

The mean volume of distribution is about 30 l/kg. The elimination half-life is 2-4 days in both plasma and tissue.

The metabolism is carried out by demethylation, hydroxylation and hydrolysis.
Plasma clearance is about 600 ml/min. The principal elimination of azithromycin is done via
the liver. High concentrations of unchanged substance have been found in the bile together
with numerous microbiologically inactive metabolites. Approximately 12% of an
intravenously administered dose is excreted unchanged in urine within 3 days following the
administration, the main part during the first 24 hours.

There is nothing indicating a change in pharmacokinetics for azithromycin in patients with
mild renal insufficiency (creatinine clearance >40 ml/min) compared with those having a
normal renal function. There are no pharmacokinetic data regarding the use of azithromycin in
patients with more severe renal insufficiency.

The pharmacokinetics has not shown to be different at mild or moderately impaired hepatic
function.

5.3 Preclinical safety data
In animal tests, phospholipidosis was observed after intravenous administration of doses
equivalent to AUC levels up to 4 times higher than the expected clinical level. Reversible
phospholipidosis was also observed in studies with oral administration at doses equivalent to
concentrations up to 40 times higher than the expected clinical level. There are no evidences
that these findings have any relevance for humans at normal use. Other preclinical studies
regarding safety pharmacology, general toxicology and reproductive toxicology did not show
any damaging effects relevant to humans that are not already described in other parts of the
summary of product characteristics. Azithromycin was negative in tests for genotoxicological
potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Citric acid monohydrate (for PH adjustment)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities
This medicinal product must not be mixed or co-administered with other medicinal products
except those mentioned in section 6.6.

6.3 Shelf life
2 years.

Chemical and physical in-use stability for reconstituted concentrate has been demonstrated for
24 hours at 25°C or 7 days in refrigerator at 2-8°C.

After reconstitution and dilution, the mixed solution is chemically and physically stable for 24
hours at 30°C or 7 days in refrigerator (at 2-8°C).

However, from a microbiological point of view, unless the method of opening/ reconstitution/
dilution precludes the risk of microbial contamination, the product should be used
immediately.

If the product is not used immediately, in-use storage times and conditions are the
responsibility of the user.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.
6.5 **Nature and contents of container**

Clear, type I glass vial of a 14 ml nominal capacity, with a bromobutyl rubber stopper and aluminium/polypropylene flip off seal.

6.6 **Special precautions for disposal**

Azithromycin 500 mg Powder for Solution for Infusion is distributed in 14 ml single use injection vials with 500 mg substance.

**Instruction for preparation of infusion**

Step 1

Prepare the initial solution infusion concentrate by adding 4.8 ml of sterile water for injection to the injection vial of Azithromycin 500 mg Powder for Solution for Infusion. Shake the vial until all of the powder is dissolved. One ml of the reconstituted solution contains 100 mg azithromycin. A clear and colourless solution is obtained.

Step 2

Dilute the resulting 5 ml infusion concentrate further with a compatible infusion solution to obtain the final solution for infusion containing azithromycin with a concentration of 1 mg/ml or 2 mg/ml (see Table 1 below).

<table>
<thead>
<tr>
<th>Concentration of final infusion solution (mg/ml)</th>
<th>Quantity of diluent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/ml</td>
<td>500 ml</td>
</tr>
<tr>
<td>2 mg/ml</td>
<td>250 ml</td>
</tr>
</tbody>
</table>

**Infusion concentrate may be diluted with:**

- 0.9 % sodium chloride
- 0.45% sodium chloride
- 5 % glucose
- 5 % glucose in 0.45% sodium chloride with 20mEq KCL
- 5 % glucose in 0.3% sodium chloride
- 5 % glucose in 0.45 sodium chloride
- 4% glucose, 0.18% sodium chloride and 0.15% potassium chloride

Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter. Only clear solutions free from particles should be used. If the solution contains particulate matter, it should be discarded.

This product is for single use only. Unused product must be discarded. Any unused product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**

PLIVA Pharma Limited
Vision House
Bedford Road
Petersfield, Hampshire, GU32 3QB
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**

PL 10622/0306
PRODUCT INFORMATION LEAFLET – text version

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

Azithromycin 500mg Powder for Solution for Infusion
(Azithromycin)

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- 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.

In this leaflet:
1. What is Azithromycin 500mg Powder for Solution for Infusion used for?
2. Before you are given Azithromycin 500mg Powder for Solution for Infusion.
3. How Azithromycin 500mg Powder for Solution for Infusion is given?
4. Possible side effects.
5. How to store Azithromycin 500mg Powder for Solution for Infusion?
6. Further information.

1. What is Azithromycin 500mg Powder for Solution for Infusion used for?

Azithromycin is one of a group of antibiotics called macrolides.

This medicine is used to treat the following serious infections when these require admission to hospital and when the infection is caused by microorganisms that are susceptible to azithromycin:

- Pneumonia acquired outside of hospital
- Infection of the internal female sex organs (Pelvic Inflammatory Disease)

This medicinal product is used when you require treatment by intravenous infusion (a ‘drip’).

This medicine is ready to be reconstituted (dissolved in liquid) to be given by infusion (a ‘drip’). See under “How Azithromycin 500mg Powder for Solution for Infusion is given.”

2. Before you are given Azithromycin 500mg Powder for Solution for Infusion

You should not be given this medicine if you:
- have ever had an allergic reaction to this medicinal product or any other macrolide antibiotic such as erythromycin.
- are taking any ergot derivatives such as ergotamine (used to treat migraine).

You should take special care with this medicine if you:
- have kidney problems
- have liver problems
- have any heart conditions
- have diarrhoea

Tell your doctor or nurse BEFORE you are given this medicine. You may need to be given another medicine instead.
Taking other medicines
Tell your doctor or nurse BEFORE you are given this medicine if you are taking, or have recently taken, any of the following medicines:
- Ergot derivatives such as ergotamine (to treat migraine)
- Nelfinavir (used in the treatment of HIV infection)
- Antacids (for indigestion)
- Rifabutin (to treat infections including tuberculosis)
- Warfarin or any similar medicine to prevent blood clots
- Ciclosporin (used following organ transplants)
- Digoxin (used to treat heart conditions)
- Astemizole (for hay fever or allergies)
- Piromozide (for psychiatric disorders)
- Theophylline (for asthma or chronic obstructive pulmonary disease)

Please tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
You should not be given this medicine if you are pregnant or are breast feeding unless your doctor has specifically recommended it. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
However, side effects could occur which may influence your ability to drive or use machines (see section 4). You are advised not to drive or use machines whilst taking azithromycin.

Important information about some of the ingredients of this medicine
This medicinal product contains 114mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

3. How Azithromycin 500mg Powder for Solution for Infusion is given?

This medicine will be given to you by your doctor or nurse as an intravenous infusion (a 'drip').

It will be given either over 3 hours with a concentration of 1mg/ml, or over 1 hour with a concentration of 2mg/ml.

Do not give this medicine in concentrations higher than 2mg/ml as it may result in pain and discomfort at the infusion site.

This medicine should not be given over a period less than 1 hour.

Do not inject this medicine directly into a vein or muscle.

Pneumonia acquired outside of hospital:
Adults and the elderly: 500mg as an intravenous infusion once daily for at least two days, followed by 500mg of oral azithromycin as a single daily dose to complete a 7 to 10 day treatment in total.

Pelvic Inflammatory Disease (infection of the internal female sex organs):
Adults and the elderly: 500mg as an intravenous infusion once daily, followed by 250mg of oral azithromycin as a single daily dose to complete a 7-10 day treatment in total.

The doctor will decide when to change to treatment using oral azithromycin.

Children: The use of this medicine in children and adolescents under 16 years has not been established.

If you have kidney problems:
Your doctor may need to reduce the dose of Azithromycin 500mg Powder for Solution for Infusion.

If you are given more Azithromycin 500mg Powder for Solution for Infusion than you should
As you will be given Azithromycin 500mg Powder for Solution for Infusion by a doctor or nurse, you are unlikely to be given the wrong dose. However, if you experience bad side effects or think you have been given too much, tell your doctor immediately.

An antimicrobial agent with anaerobic activity should be administered in combination with azithromycin if anaerobic microorganisms are suspected of contributing to the infection.

The safety of intravenous azithromycin has not been assessed beyond the time frames described in the clinical trials of use in patients with community-acquired pneumonia and pelvic inflammatory disease.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects are important and will require immediate action if you experience them. You should stop taking azithromycin and see your doctor immediately if the following symptoms occur:

Rare side effects affect fewer than 1 in 1,000 patients
- Swelling of the face, tongue and windpipe which can cause great difficulty in breathing
- A sudden allergic reaction with shortness of breath, rash, wheezing and drop of blood pressure
- Severe, extensive, blistering skin rash
- Watery and severe diarrhoea that may also be bloody

The following side effects may also occur:

Common – more than 1 in every 100 people taking this medicine:
- Local pain and inflammation at infusion site
- Stomach pain, diarrhea, feeling sick, indigestion or heartburn, vomiting,
- Altered blood test results of liver function

Uncommon – less than 1 in every 100 but more than 1 in every 1000 people taking this medicine:
- Headache, drowsiness
- Taste disturbance, flatulence (wind)
- Skin rash and itching, oedema (build-up of fluid in the body tissues)
- Yeast infections of the mouth and/or vagina.

Rare - less than 1 in every 1000 but more than 1 in every 10000 people taking this medicine:
- Feeling weak, fatigue, dizziness, tingling sensations, fainting, discomfort, nervousness, aggression, convulsions (fits), hyperactivity, deafness or ringing in the ears (effects on hearing are usually reversible)
- A reduced number of cells in the circulation that fight infection leading to frequent infections such as sore throats, mouth ulcers, bleeding or bruising more easily than normal
- Rapid or irregular heart beat, alterations in the electrical activity of the heart
- Loss of appetite, discoloration of tongue, constipation, loose stools, inflammation of the pancreas causing pain in the abdomen and vomiting, hives, increased sensitivity to sunlight
- Inflammation of the liver and jaundice (yellowing of the skin and the whites of the eyes), liver failure (rarely life-threatening)
- Joint pain
- Kidney problems
- Visual problems
- Inflammation of the vagina (vaginitis)

If you experience any of these side effects, or you notice any not listed in this leaflet, please tell your doctor or nurse.

5. How to store Azithromycin 500mg Powder for Solution for Infusion?

For the unopened product with dry powder, this medicinal product does not require any special storage precautions.

Once the vial has been reconstituted (dissolved in liquid) ready for use, the product is stable for 24 hours when stored at temperatures lower than 30°C or for 7 days when stored in a refrigerator between 2°C and 8°C. From a microbiological point of view, the prepared solution should be used immediately. If the product is not used immediately, infuse storage times and conditions are the responsibility of the user.

Unused solution must be discarded. Medicines should not be disposed of via wastewater or household waste. Any unused product or waste material should be disposed of in accordance with local requirements.

Do not use Azithromycin 500mg Powder for Solution for Infusion after the expiry date which is stated on the label. The expiry date refers to the last day of that month. Your doctor or nurse will check that this date has not been passed.

The doctor or nurse responsible for giving you this medicine will ensure it has been reconstituted (dissolved into liquid) correctly before giving it to you.

Keep out of the reach and sight of children.

6. Further information

This medicinal product contains
The active ingredient is azithromycin. Each vial contains 500mg azithromycin as monohydrate. The other ingredients are citric acid monohydrate and sodium hydroxide.

**What Azithromycin 500mg Powder for Solution for Infusion looks like and contents of the pack.**
This medicinal product is a white to almost white powder, and is presented in a 14 ml glass vial with a rubber stopper and aluminium/polypropylene flip-off seal, packaged in a carton.

**Marketing Authorisation holder:**
PLIVA Pharma Limited, Vision House, Bedford Road, Petersfield, Hampshire, GU32 3QB, United Kingdom.

**Manufacturer:**
Pliva Krakow S.A.; 80 Mogilska str.; 31-546 Krakow; Poland

**This leaflet was last revised in:** August 2010

PL 10622/0306

---

**Prescriber Information**

**Azithromycin 500 mg Powder for Solution for Infusion**

The following information is intended for medical or healthcare professionals only

(Please note this is a Prescriber Information Leaflet NOT the Summary of Product Characteristics (SPC). For full details regarding this product please refer to the SPC).

**Administration**
This medicinal product is administered as an intravenous infusion over 3 hours with a concentration of 1 mg/ml, or over 1 hour with a concentration of 2 mg/ml. Higher concentrations should be avoided as all tested subjects receiving infusion concentrations higher than 2 mg/ml experienced local reactions at the infusion site.

The azithromycin infusion time should not be shorter than 60 minutes.

Azithromycin should not be given as a bolus or intramuscular injection.

**Incompatibilities**
This medicinal product must not be mixed or co-administered with other medicinal products except those mentioned under the ‘Infusion concentrate may be diluted with’ subheading below.

**Instructions for preparation of infusion**

**Step 1**
Prepare the initial solution infusion concentrate by adding 4.8 ml of sterile water for injection to the injection vial of Azithromycin 500 mg Powder for Solution for Infusion. Shake the vial until all of the powder is dissolved. One ml of the reconstituted solution contains 100 mg azithromycin. A clear and colourless solution is obtained.

**Step 2**
Dilute the resulting 5 ml infusion concentrate further with a compatible infusion solution to obtain the final solution for infusion containing azithromycin with a concentration of 1 mg/ml or 2 mg/ml (see Table 1 below).

**Table 1 Preparation of final infusion solution**

<table>
<thead>
<tr>
<th>Concentration of final infusion solution (mg/ml)</th>
<th>Quantity of diluent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/ml</td>
<td>500 ml</td>
</tr>
<tr>
<td>2 mg/ml</td>
<td>250 ml</td>
</tr>
</tbody>
</table>

**Infusion concentrate may be diluted with**
- 0.9% sodium chloride
- 0.45% sodium chloride
- 5% glucose
- 5% glucose in 0.45% sodium chloride with 20mEq KCL
- 5% glucose in 0.3% sodium chloride
- 5% glucose in 0.45 sodium chloride
- 4% glucose, 0.18% sodium chloride and 0.15% potassium chloride

Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter. Only clear solutions free from particles should be used. If the solution contains particulate matter, it should be discarded.

This product is for single use only. Unused product must be discarded. Any unused product or waste material should be disposed of in accordance with local requirements.

**Special precautions for storage**
This medicinal product does not require any special storage conditions.

For storage conditions of the reconstituted and diluted medicinal product, see below.

Chemical and physical in-use stability for reconstituted concentrate has been demonstrated for 24 hours at 25°C or 7 days in refrigerator at 2-8°C.

After reconstitution and dilution, the mixed solution is chemically and physically stable for 24 hours at 30°C or 7 days in refrigerator (at 2-8°C).

However, from a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.

If the product is not used immediately, in-use storage times and conditions are the responsibility of the user.
### LABELLING – text version

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

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTON</td>
</tr>
</tbody>
</table>

#### 1. NAME OF THE MEDICINAL PRODUCT

Azithromycin 500mg Powder for Solution for Infusion
Azithromycin.

#### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 500mg Azithromycin as monohydrate

#### 3. LIST OF EXCIPIENTS

Also contains citric acid monohydrate and sodium hydroxide.

See the package leaflet for further information.

#### 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

Pack sizes:
1 vial

#### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only. For intravenous infusion only
When reconstituted with 4.8ml water for injections, each ml of solution contains
100mg azithromycin

Reconstituted solution should be further diluted before use. Read the enclosed package leaflet before use

Do not use unless the prepared solution is clear.

#### 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

Discard any remaining solution.

#### 8. EXPIRY DATE

EXP:
9. **SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special storage conditions. For storage conditions of diluted product, see leaflet for further information.

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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

PLIVA Pharma Limited
Vision House, Bedford Road,
Petersfield, Hampshire,
GU32 3QB, UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 10622/0306

13. **BATCH NUMBER**

Batch No.:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Use as directed by the doctor.

16. **INFORMATION IN BRAILLE**

N/A
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial Label</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin 500mg Powder for Solution for Infusion</td>
</tr>
<tr>
<td>Azithromycin.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single use only.</td>
</tr>
<tr>
<td>For intravenous infusion only</td>
</tr>
<tr>
<td>Read the package leaflet before use. To be reconstituted and diluted.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch No:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 vial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM</td>
</tr>
<tr>
<td>MA Holder: Phiva Pharma Ltd</td>
</tr>
<tr>
<td>PL 10622/0306</td>
</tr>
</tbody>
</table>