CLARITHROMYCIN 500MG POWDER FOR SOLUTION FOR INFUSION

(CLARITHROMYCIN)

PL 24610/0005

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bowmed Limited a Marketing Authorisation (licence) for the medicinal product Clarithromycin 500mg Powder for Solution for Infusion (PL 24610/0005) on 23rd January 2008. This is an antibiotic prescription-only medicine (POM) used to treat various types of infection.

Clarithromycin 500mg Powder for Solution for Infusion contains the active ingredient clarithromycin, which belongs to a group of medicines called 'macrolide antibiotics'. Clarithromycin infusion is used to treat chest infections such as bronchitis or pneumonia, throat or sinus infections, and skin or soft tissue infections.

Clarithromycin infusion will usually be given by a doctor or nurse by an intravenous infusion ('drip'). The infusion is prepared by dissolving the powder in sterile water. The solution obtained is added to a larger volume of sterile liquid, and this is then infused (like being given a blood transfusion) into one of your veins.

The proposed product was considered to be a generic version of the reference product Klaricid IV 500mg (PL 00037/0251, Abbott Laboratories Ltd).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Clarithromycin 500mg Powder for Solution for Infusion outweigh the risk; hence a Marketing Authorisation has been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bowmed Limited a Marketing Authorisation for the medicinal product Clarithromycin 500mg Powder for Solution for Infusion (PL 24610/0005) on 23rd January 2008. The product is a prescription-only medicine (POM).

The application was submitted as a national, abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended. The application refers to the innovator product, Klaricid IV 500mg (PL 00037/0251), marketed by Abbott Laboratories Ltd and authorised on 22 September 1993.

The active ingredient, clarithromycin, belongs to the macrolide group of antibiotics. Its antibiotic activity is especially effective in the treatment of upper and lower respiratory tract infections, skin infections and infections produced by *Mycobacterium avium*. It is also used together with other antibiotics in the eradication of *Helicobacter pylori.*

Clarithromycin 500mg Powder for Solution for Infusion is indicated whenever parenteral therapy is required for treatment of infections caused by susceptible organisms in lower respiratory tract infections such as acute and chronic bronchitis, and pneumonia; upper respiratory tract infections, for example, sinusitis and pharyngitis; and skin and soft tissue infections.

PHARMACEUTICAL ASSESSMENT

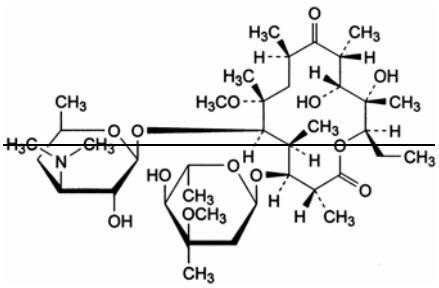
ACTIVE SUBSTANCE

Clarithromycin

Nomenclature:

INN:	Clarithromycin
Chemical name:	(3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-a-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-12,13-dihydroxy-7-methoxy-3,5,7,9,11, 13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-b-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione

Structure:



Molecular formula:	$C_{38}H_{69}NO_{13}$
Molecular weight:	748
CAS No:	81103-11-9

Physical form:	A white or almost white crystalline powder
Solubility:	Practically insoluble in water, soluble in acetone and in methylene chloride, slightly soluble in methanol

The active substance, clarithromycin, is the subject of a European Pharmacopeia monograph.

The manufacture and quality of the active substance, manufactured by the active substance manufacturer, are controlled by a Certificate of Suitability (CEP). Confirmation has been provided that the materials used in the synthesis of the active substance are not derived from animals or animals susceptible to BSE and TSE and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided which is in line with the European Pharmacopeia (Ph. Eur.) monograph specification and CEP.

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 specification.

The active substance, clarithromycin (a microfine powder), is stored in appropriate packaging. It is packed in polyethylene bags which are sealed and placed into aluminium foil bags which are thermally closed. These aluminium foil bags are then placed into a box which is strapped and wrapped with plastic. Specifications and Certificates of Analysis for all packaging components used have been provided. The

polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed packaging. This data demonstrates the stability of the active substance and a suitable retest period has been set based on the data.

DRUG PRODUCT

Composition

A vial of lyophilised powder contains 500mg of the active substance, clarithromycin. Other ingredients consist of pharmaceutical excipients, namely lactobionic acid and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. 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.

There were no novel excipients used and no overages.

Impurity profiles

The impurities were within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

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

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specification is satisfactory and complies with the requirements of the Ph. Eur. monograph. 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. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The drug product is packed in Ph. Eur. Type II transparent glass vials of size 20ml. The vials are sealed with Ph. Eur. bromobutyl rubber stoppers and aluminium flip-off caps. The vials are packaged individually, with the product information leaflet, in cardboard outer cartons.

All primary packaging satisfies Directive 2002/72/EC (as amended), and is suitable for contact with parenteral preparations. Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, with storage instructions 'Store below 25°C'. This is satisfactory. For storage conditions of the reconstituted medicinal product, refer to the SPC.

Bioequivalence Study

Bioequivalence studies are not necessary to support this application for a parenteral product.

EXPERT REPORT

The quality overview is written by an appropriately qualified expert and is satisfactory. A satisfactory Curriculum Vitae has been provided for the pharmaceutical expert.

PRODUCT INFORMATION:

Summary of Product Characteristics

The approved SPC is satisfactory.

Patient Information Leaflet

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

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

Conclusion

The proposed product, Clarithromycin 500mg Powder for Solution for Infusion, has been shown to be a generic version of the reference product, Klaricid IV 500mg, 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 UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

The quality grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted.

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Clarithromycin 500mg Powder for Solution for Infusion is indicated whenever parenteral therapy is required for treatment of infections caused by susceptible organisms in the following conditions:

- Lower respiratory tract infections, for example, acute and chronic bronchitis, and pneumonia
- Upper respiratory tract infections, for example, sinusitis and pharyngitis
- Skin and soft tissue infections

CLINICAL PHARMACOLOGY

No new data are submitted and none are required for this type of application.

EFFICACY

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

Clarithromycin 500mg Powder for Solution for Infusion is to be administered as an aqueous intravenous solution and contains the same active substance, in the same concentration, as the currently authorised reference product Klaricid IV 500mg. Thus, in accordance with the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", (CPMP/EWP/QWP/1401/98), 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 expert report.

EXPERT REPORT

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSION

The grounds for establishing the proposed product as a generic version of the reference product, Klaricid IV 500mg (PL 00037/0251), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. When used as indicated, Clarithromycin 500mg Powder for Solution for Infusion has a favourable benefit-to-risk ratio. Therefore, the grant of a Marketing Authorisation is recommended on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Clarithromycin 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.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

The applicant's Clarithromycin 500mg Powder for Solution for Infusion (PL 24610/0005) has been demonstrated to be a generic version of the reference product Klaricid IV 500mg (PL 00037/0251, Abbott Laboratories Ltd).

No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE

The approved SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

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

The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with clarithromycin is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on 19th June 2006

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 16th August 2006

3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 7th December 2006

4 The applicant responded to the MHRA's request, providing further information for the quality sections on 5th July 2007

5 The application was determined on 23rd January 2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Clarithromycin 500mg Powder for Solution for Infusion is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 500mg Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500mg clarithromycin.

When reconstituted, the solution strength is 2mg/ml (see section 6.6).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

White or almost white powder

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Clarithromycin 500 mg Powder for Solution for Infusion is indicated whenever parenteral therapy is required for treatment of infections caused by susceptible organisms in the following conditions:

- Lower respiratory tract infections for example, acute and chronic bronchitis, and pneumonia.

- Upper respiratory tract infections for example, sinusitis and pharyngitis.

- Skin and soft tissue infections.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

For intravenous administration only.

Intravenous therapy may be given for 2 to 5 days and should be changed to oral clarithromycin therapy when appropriate.

Adults:

The recommended dosage is 1.0 gram daily, divided into two 500mg doses, appropriately diluted as described below (see section 6.6).

Children: At present, there are insufficient data to recommend a dosage regimen for routine use in children.

Elderly: As for adults.

Renal impairment: In patients with renal impairment who have creatinine clearance less than 30ml/min, the dosage of clarithromycin should be reduced to one half of the normal recommended dose.

Recommended administration:

Clarithromycin 500mg Powder for Solution for Infusion should be administered into one of the larger proximal veins as an IV infusion over 60 minutes, using a solution concentration of about 2mg/ml. Clarithromycin should not be given as a bolus or an intramuscular injection.

For instructions on reconstitution and dilution, see section 6.6. The reconstituted product is a clear solution.

4.3 CONTRAINDICATIONS

Clarithromycin is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs.

Clarithromycin 500mg Powder for Solution for Infusion and ergot derivatives should not be co-administered (see section 4.5).

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels have been reported in patients receiving either of these drugs and clarithromycin concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see Section 4.5).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Clarithromycin is principally excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic and renal function.

Prolonged or repeated use of clarithromycin may result in an overgrowth of non-susceptible bacteria or fungi. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Clarithromycin has been shown not to interact with oral contraceptives.

As with other macrolide antibiotics the use of clarithromycin in patients concurrently taking drugs metabolised by the cytochrome P450 system (e.g. warfarin, ergot alkaloids, triazolam, midazolam, disopyramide, lovastatin, rifabutin, phenytoin, cyclosporin and tacrolimus) may be associated with elevations in serum levels of these other drugs. Rhabdomyolysis, co-incident with the co-administration of clarithromycin, and HMG-CoA reductase inhibitors, such as lovastatin and simvastatin has been reported.

The administration of clarithromycin to patients who are receiving theophylline has been associated with increased serum theophylline levels and potential theophylline toxicity.

The use of clarithromycin in patients receiving warfarin may result in a potentiation of the effects of warfarin. Prothrombin time should be frequently monitored in these patients.

The effects of digoxin may be potentiated with concomitant administration of clarithromycin. Monitoring of serum digoxin levels should be considered.

Clarithromycin may potentiate the effects of carbamazepine due to a reduction in the rate of excretion.

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV infected adults may result in decreased steady-state zidovudine concentrations. Since this interaction in adults is thought to be due to interference of clarithromycin with simultaneously administered oral zidovudine, this interaction should not be a problem when clarithromycin is administered intravenously. With oral clarithromycin, the interaction can be largely avoided by staggering the doses; see Summary of Product Characteristics for Clarithromycin tablets for further information. No similar reaction has been reported in children.

Ritonavir increases the area under the curve (AUC), C_{max} and C_{min} of clarithromycin when administered concurrently. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CL_{CR} 30 to 60ml/min the dose of clarithromycin should be decreased by 50%. For patients with CL_{CR} <30ml/min the dose of clarithromycin should be decreased by

75%. Doses of clarithromycin greater than 1g/day should not be co-administered with ritonavir.

There have been post-marketed reports of Torsade de Pointes occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Levels of these medications should be monitored during clarithromycin therapy. Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity (see Section 4.4).

Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischaemia of the extremities and other tissues including the central nervous system (see section 4.3 Contraindications).

4.6 PREGNANCY AND LACTATION

The safety of clarithromycin during pregnancy and breast feeding of infants has not been established. Clarithromycin should thus not be used during pregnancy or lactation unless the benefit is considered to outweigh the risk.

Some animal studies have suggested an embryotoxic effect but only at dose levels which are clearly toxic to mothers. Clarithromycin has been found in the milk of lactating animals and in human breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None reported

4.8 UNDESIRABLE EFFECTS

The most frequently reported infusion-related adverse events in clinical studies were injection-site inflammation, tenderness, phlebitis and pain. The most common non-infusion related adverse event reported was taste perversion.

During clinical studies with oral clarithromycin, the drug was generally well tolerated. Side-effects included nausea, vomiting, diarrhoea, dyspepsia and abdominal pain and paraesthesia. Stomatitis, glossitis and oral monilia have been reported. Other side-effects include headache, tooth and tongue discolouration, arthralgia, myalgia and allergic reactions ranging from urticaria, mild skin eruptions and angioedema to anaphylaxis and, rarely, Stevens-Johnson syndrome/ toxic epidermal necrolysis. Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been received. There have been reports of transient central nervous system side-effects including dizziness, vertigo, anxiety, insomnia, bad dreams, tinnitus, confusion, disorientation, hallucinations, psychosis, and depersonalisation. There have been reports of hearing loss with clarithromycin which is usually reversible upon withdrawal of therapy.

Pseudomembranous colitis has been reported rarely with clarithromycin, and may range in severity from mild to life threatening.

There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin.

There have been very rare reports of uveitis mainly in patients treated with concomitant rifabutin, most of these were reversible.

Isolated cases of leukopenia and thrombocytopenia have been reported.

As with other macrolides, hepatic dysfunction (which is usually reversible) including altered liver function tests, hepatitis and cholestasis with or without jaundice, has been reported. Dysfunction may be severe and very rarely fatal hepatic failure has been reported.

Cases of increased serum creatinine, interstitial nephritis, renal failure, pancreatitis and convulsions have been reported rarely.

As with other macrolides, QT prolongation, ventricular tachycardia and Torsade de Pointes have been rarely reported with clarithromycin.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see sections 4.4 and 4.5).

4.9 OVERDOSE

There is no experience of overdosage after IV administration of clarithromycin. However, reports indicate that the ingestion of large amounts of clarithromycin orally can be expected to produce gastro-intestinal symptoms. Adverse reactions accompanying overdosage should be treated by gastric lavage and supportive measures.

As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeuic group: Antibiotics macrolides

ATC code: J01F A09

Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. Clarithromycin demonstrates excellent *in vitro* activity against standard strains of clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic gram positive and negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

The 14-(R)-hydroxy metabolite of clarithromycin, formed in man by first pass metabolism also has anti-microbial activity. The MICs of this metabolite are equal to or two-fold higher than the MICs of the parent compound except for H. influenzae where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Clarithromycin 500 mg Lyophilisate for Solution for Injection is usually active against the following organisms *in vitro*:

Gram-positive Bacteria:

Staphylococcus aureus (methicillin susceptible); Streptococcus pyogenes (Group A beta-haemolytic streptococci); alpha-haemolytic streptococcus (viridans group); Streptococcus (Diplococcus) pneumoniae; Streptococcus agalactiae; Listeria monocytogenes.

Gram-negative Bacteria:

Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae; Legionella pneumophila, Bordetella pertussis, Helicobacter pylori; Campylobacter jejuni.

Mycoplasma:

Mycoplasma pneumoniae; Ureaplasma urealyticum.

Other Organisms:

Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae; Chlamydia pneumoniae.

Anaerobes:

Macrolide-susceptible Bacteriodes fragilis; Clostridium perfringens; Peptococcus species; Peptostreptococcus species; Propionibacterium acnes.

Clarithromycin has bactericidal activity against several bacterial strains. These organisms include H. influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Morazella (Brahamella) catarrhalis, Neisseria gonorrhoeae, Helicobacter pylori and Campylobacter spp.

The activity of clarithromycin against H. pylori is greater at neutral pH than at acid pH.

5.2 PHARMACOKINETIC PROPERTIES

The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism as indicated by lower bioavailability of the metabolite following IV administration. Following IV administration, the blood levels of clarithromycin achieved are well in excess of the MIC 90s for the common pathogens and the levels of 14-hydroxyclarithromycin exceed the necessary concentrations for important pathogens, e.g. H. influenzae.

The pharmacokinetics of clarithromycin and the 14-hydroxy metabolite are non-linear; steady state is achieved by day 3 of IV dosing. Following a single 500mg IV dose over 60 minutes, about 33% clarithromycin and 11% 14-hydroxyclarithromycin is excreted in the urine at 24 hours.

5.3 PRECLINICAL SAFETY DATA

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactobionic acid

Water for injections

6.2 INCOMPATIBILITIES

Clarithromycin 500mg Powder for Solution for Infusion should only be diluted with the diluents recommended in section 6.6.

6.3 SHELF LIFE

Unopened vial: 36 months.

Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 5 - 25ºC when reconstituted in 10ml water for injections, and for 6 hours (at 25ºC) or 24 hours at (5ºC) once diluted in 250ml of appropriate diluent (see section 6.6).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C

6.5 NATURE AND CONTENTS OF CONTAINER

Ph. Eur Type II clear glass 20ml vial with bromobutyl stopper and aluminium flip-off cap.

Carton contains one vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Reconstitute each vial of Clarithromycin 500mg Lyophilisate for Solution for Infusion with 10ml sterile water for injections.

The reconstituted solution can be diluted in 250ml of the following diluents:

0.9% sodium chloride solution

5% dextrose solution

5% dextrose in 0.3% or 0.45% sodium chloride solution

5% dextrose in Ringers solution

5% dextrose in Ringers Lactate solution

Clarithromycin 500mg Lyophilisate for Solution for Infusion should be administered into one of the larger proximal veins as an IV infusion over 60 minutes, using a solution concentration of about 2mg/ml. Clarithromycin should not be given as a bolus or an intramuscular injection.

For single use only. The vial and any unused solution should be adequately disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bowmed Limited,

113 Promenade

Cheltenham GL50 1NW

8 MARKETING AUTHORISATION NUMBER(S)

PL 24610/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/01/2008

10 DATE OF REVISION OF THE TEXT

23/01/2008

PRODUCT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Clarithromycin 500mg Powder for Solution for Infusion

Clarithromycin

Pharmacode

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 your pharmacist.
- 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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

In this leaflet:

The name of your medicine is "Clarithromycin 500mg Powder for Solution for Infusion" (referred to as Clarithromycin Infusion throughout this leaflet).

1. WHAT CLARITHROMYCIN INFUSION IS AND WHAT IT IS USED FOR

Your medicine contains the active substance clarithromycin, which is one of a group of medicines called "macrolide antibiotics". These are used to kill the bacteria or 'germs' that cause infections.

Your doctor has decided to give you Clarithromycin Infusion to treat:
- A chest infection such as bronchitis or pneumonia
- A throat or sinus infection
- A skin or soft tissue infection.

2. BEFORE YOU ARE GIVEN CLARITHROMYCIN INFUSION

Do not take Clarithromycin Infusion:
- If you are allergic (hypersensitive) to clarithromycin
- If you are allergic to any of the other ingredients of Clarithromycin Infusion (see section 6 "Further Information")
- If you are allergic to any other macrolide antibiotics such as erythromycin or azithromycin.

If you are unsure, talk to your doctor or nurse.

Before treatment with Clarithromycin Infusion you should tell your doctor:
- If you have liver or kidney problems.

Taking other medicines:
Do not take Clarithromycin Infusion if you are taking any of the following medicines:
- Ergotamine or dihydroergotamine (for migraine headaches)
- Cisapride (for stomach problems)
- Terfenadine or astemizole (for hayfever or allergies)
- Pimozide (for schizophrenia)
- Colchicine (usually taken for gout).

Tell your doctor or nurse if you are taking any of the following medicines:
- Digoxin, disopyramide or quinidine (medicines for certain heart conditions)
- Warfarin (used to "thin" the blood)
- Carbamazepine or phenytoin (for epilepsy)
- Theophylline (used to treat asthma)
- Triazolam or midazolam (make you feel sleepy before an operation)
- Simvastatin or lovastatin (used to reduce cholesterol)
- Cyclosporine (suppresses the immune system)
- Zidovudine (anti-viral agent)
- Ritonavir (anti-HIV medicine)
- Rifabutin (used to treat some infections)
- Tacrolimus (for organ transplants).

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:
If you are pregnant, likely to become pregnant or are breast-feeding, you must tell your doctor or nurse before you are given this medicine.

Driving and using machines
This medicine has no known effects on the ability to drive or use machines.

3. HOW CLARITHROMYCIN INFUSION IS GIVEN

Clarithromycin Infusion will usually be given by a doctor or nurse by an intravenous infusion ('drip').
The infusion is prepared by dissolving the powder in sterile water. The solution obtained is added to a larger volume of sterile liquid, and this is then infused (like being given a blood transfusion) into one of your veins for at least an hour.

Adults and children over 12 years:
The usual adult dose is 1 gram per day given in two doses, for two to five days. Patients with kidney problems may be given a smaller dose.
The correct dose will be decided by your doctor.

Children under 12 years:
Children should not be given Clarithromycin Infusion.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Clarithromycin Infusion can cause side effects, although not everybody gets them.

If you get any of the following side effects soon after receiving this medicine, tell your doctor or nurse immediately. If you get them, you may have had a serious allergic reaction or other type of reaction to this medicine. You may need urgent medical attention:

- Skin rash and itching
- Peeling, blistering or crusting of the skin
- Ulcers on the skin or in the mouth
- Any sudden wheeziness, difficulty in breathing
- Yellow colouration of the skin or the eyes.

If you develop severe or prolonged diarrhoea, which may have blood or mucus in it, tell your doctor or nurse immediately.

Other side effects that can occur:

- Nausea (feeling sick), vomiting (being sick), tummy pain, and diarrhoea
- Pain, inflammation, itching or swelling at the site of injection
- Numbness or a feeling of "pins and needles"
- Headache, joint pain or muscle pain
- Changes in liver function tests
- Kidney problems
- Changes in sense of taste and smell
- Discoloured teeth (which can be removed by professional dental cleaning)
- Swelling or darkening of the tongue, sore mouth and "thrush" in the mouth
- Temporary loss of hearing
- Dizziness, loss of bearings, "ringing" in the ears
- Difficulty sleeping, hallucinations (seeing things), bad dreams
- Confusion, change in sense of reality, and panicking
- Fainting due to low blood sugar
- Mood and behavioural disorders
- Unexpected bruising
- Blood taking longer to clot after a cut to the skin
- Change in heart rhythm,
- Changes in the number of white blood cells
- Convulsions (fits)
- Inflammation of the pancreas.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

5. HOW TO STORE CLARITHROMYCIN INFUSION

Keep out of the reach and sight of children. Do not use Clarithromycin Infusion after the expiry date which is printed on the label and carton.
Store below 25°C. Your doctor, pharmacist or nurse will know how to store Clarithromycin Infusion properly.

6. FURTHER INFORMATION

What Clarithromycin Infusion contains

- The active substance is Clarithromycin 500mg
- The other ingredient is Lactobionic acid.

What Clarithromycin Infusion looks like and contents of the pack:
Clarithromycin Infusion is a vial containing a white to off-white powder. Each vial contains 500mg clarithromycin. Each carton contains one vial.

Marketing Authorisation Holder:
Bowmed Limited,
113 Promenade, Cheltenham GL50 1NW

Manufacturer:
Laboratorios Alcalá Farma S.L.,
Barcelona, Spain

This leaflet was last approved in MM/YYYY

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for medical or healthcare professionals only.

Instructions for use and handling:

Reconstitute each vial of Clarithromycin 500mg Powder for Solution for Infusion with 10ml sterile water for injections. The reconstituted solution can be diluted in 250ml of the following diluents:

- 0.9% sodium chloride solution
- 5% dextrose solution
- 5% dextrose in 0.3% or 0.45% sodium chloride solution
- 5% dextrose in Ringers solution
- 5% dextrose in Ringers Lactate solution.

Clarithromycin 500mg Powder for Solution for Infusion should be administered into one of the larger proximal veins as an IV infusion over 60 minutes, using a solution concentration of about 2mg/ml. Clarithromycin should not be given as a bolus or an intramuscular injection.

For single use only. The vial and any unused solution should be disposed of in accordance with local requirements.

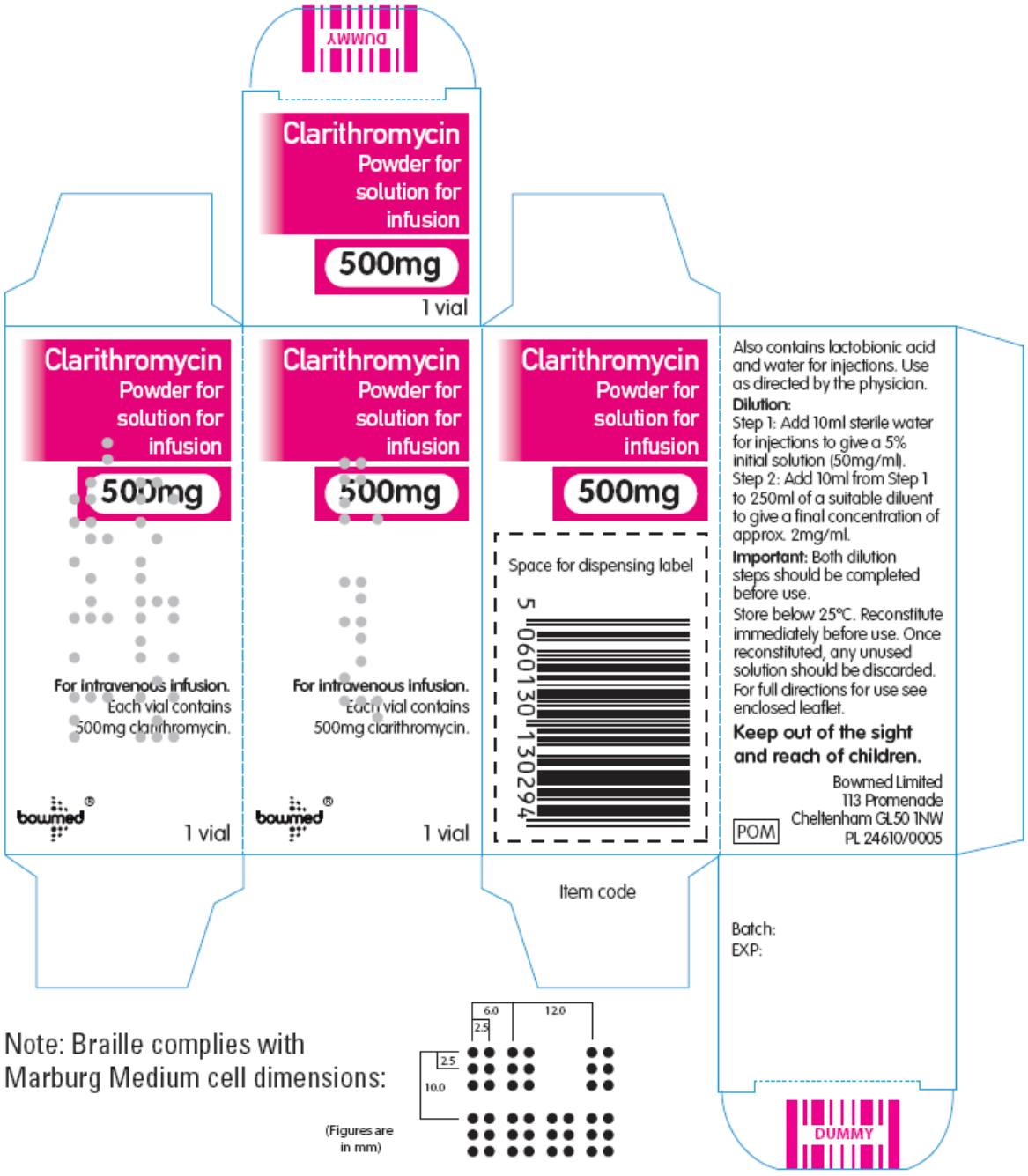
Storage precautions: Store below 25°C

Shelf life:
Unopened vial: 18 months.
Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 5 - 25°C when reconstituted in 10ml water for injections, and for 6 hours (at 25°C) or 24 hours (at 5°C) once diluted in 250ml of appropriate diluent.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

LABELLING

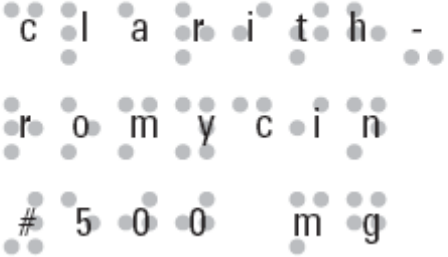
Carton with braille



Note: Braille complies with Marburg Medium cell dimensions:

(Figures are in mm)

Braille text reads as follows:



Label


Clarithromycin
500mg
Powder for infusion
For intravenous use. To be given as directed by the physician. Read package leaflet before use. Store below 25°C.
Bowmed Limited
PL: 24610/0005
POM
Batch:
EXP: