CLARITHROMYCIN 500MG/VIAL LYOPHILISATE FOR SOLUTION FOR INFUSION

UKPAR

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CLARITHROMYCIN 500MG/VIAL LYOPHILISATE FOR SOLUTION FOR INFUSION

LAY SUMMARY

On 30th October 2008, the MHRA granted Britannia Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion (PL 04483/0063). This is a prescription-only medicine (POM) for the treatment of chest infections (such as bronchitis and pneumonia), throat and sinus infections, and skin and soft tissue infections.

The active substance, clarithromycin, belongs to a group of drugs called macrolides and is an antibiotic that stops the growth of many types of "bugs" that cause infections.

No new or unexpected safety concerns arose from this applications and it was, therefore, judged that the benefits of taking Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion outweigh the risks, hence a Marketing Authorisation has been granted.

CLARITHROMYCIN 500MG/VIAL LYOPHILISATE FOR SOLUTION FOR INFUSION

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion (PL 04483/0063) to Britannia Pharmaceuticals Limited on 30th October 2008. The product is a prescription-only medicine for the parenteral treatment of infections caused by susceptible organisms in the following conditions:

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

This was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, referring to the original product Klaricid IV, which was originally authorised to Abbot Laboratories Limited in 1993.

Clarithromycin, is a semisynthetic derivative of erythromycin [6-O-methyl erythromycin-A], which is a macrolide antibiotic that is active against aerobic and anaerobic bacteria both gram positive and gram negative. Its primary efficacy is against respiratory tract infections, soft tissue infections and *H. pylori* bacteria.

No new preclinical or clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. Assurances have been provided that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has also been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

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

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

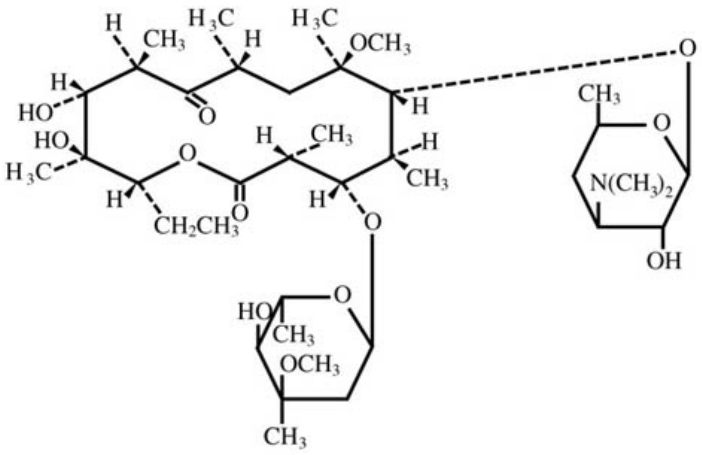
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Clarithromycin

rINN: Clarithromycin

Structure:



Formula: $C_{38}H_{69}NO_{13}$

Chemical names: 6-(4-dimethylamino-3-hydroxy- 6-methyl-tetrahydropyran-2-yl) oxy-14-ethyl-12,13-dihydroxy-4-(5-hydroxy-4-methoxy-4,6- dimethyl-tetrahydropyran-2-yl) oxy-7-methoxy-3,5,7,9,11, 13-hexamethyl-1-oxacyclotetradecane-2,10-dione

MW: 747.95

Clarithromycin is a white to off-white crystalline powder, practically insoluble in water, soluble in acetone and dichloromethane, slightly soluble in methanol.

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

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) certificate of suitability.

Satisfactory certificates of analysis have been provided for batches of active clarithromycin, in-line with the proposed specifications on the certificate of suitability.

The active substance is stored in low-density polyethylene bags, which are sealed inside an aluminium tin, polypropylene drum or a high-density polyethylene drum. Suitable specifications have been provided for all packaging used and these have been show to comply with European Directive 2002/72/EC, concerning contact with food.

Suitable stability data have been provided for active clarithromycin, stored in the proposed packaging. Based on these data, a retest period of 3 years has been provided.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of pharmaceutical excipients, namely lactobionic acid and sodium hydroxide. Sodium hydroxide complies with its relevant European Pharmacopoeia monograph. Lactobionic acid is manufactured from lactobionic acid, water for injections and sodium hydroxide, all of which are of pharmacopoeial grade.

None of the excipients used contain material of animal or human origin.

Pharmaceutical Development

The objective of the development programme was to produce a generic medicinal product similar to Klaricid IV (Abbot Laboratories Limited, UK).

A suitable pharmaceutical development programme has been submitted.

Comparable impurity and assay profiles have been provided for both the proposed product and the originator product.

Manufacture

A description and flow-chart of the manufacturing method has been provided. A satisfactory batch formula has been provided for manufacture of the maximum batch size. Satisfactory in-process controls are in place, based on process validation data and controls on the finished product.

Finished Product Specification

The finished product specification provided is satisfactory. 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 working standards used.

Container Closure System

The finished product is packaged in a 15ml clear Type 1 glass vial sealed with a 20mm grey bromobutyl Type 1 lyophilisation stopper. This is protected by a 20mm cap that is silver in colour, with a red ring on the top surface that incorporates a transparent flip-off plastic top. The product is supplied in packs of 1 vial.

Suitable specifications and certificates of analysis for all packaging types used have been provided. The primary packaging has been shown to comply with current guidelines concerning materials that are in contact with parenteral solutions.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months has been set for the unopened product, with no storage conditions. In terms of stability, once reconstituted, the following instructions are given:

Once reconstituted chemical and physical in-use stability has been demonstrated for 24 hours (at 5ºC to 25ºC) when reconstituted in 10ml of water for injections and for 6 hours (at 25ºC) or 24 hours (at 5ºC) once diluted in 250ml of an appropriate infusion solution.

From a microbiological point of view the product should be used immediately. If not used immediately the 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 2ºC to 8º C unless the reconstitution and dilution has taken place in controlled and validated aseptic conditions.

ADMINISTRATIVE INFORMATION

MAA Form

The MAA form is pharmaceutically satisfactory.

Pharmaceutical Expert Report

A pharmaceutical expert report has been submitted, written by an appropriately qualified person. It is a suitable summary of the pharmaceutical aspects of the dossier.

Summary of Product Characteristics (SPC)

The SPC is pharmaceutically satisfactory.

Patient Information Leaflet (PIL)

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.

Packaging

The packaging is pharmaceutically satisfactory.

CONCLUSION

It is recommended that a Marketing Authorisation is granted for this application.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, and the similar impurity profiles.

PRECLINICAL ASSESSMENT

This application for a generic medicinal product refers to Klaricid IV (Abbot Laboratories Limited, UK), which has been licensed within the EEA for over 10 years. 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 an appropriately qualified person. It is a suitable summary of the preclinical aspects of the dossier.

CLINICAL ASSESSMENT

1. TOXICOLOGY
No new pre-clinical data have been provided.

2. CLINICAL PHARMACOLOGY
No new data are submitted and none are required for this type of application. A bioequivalence study is not required, in accordance with CPMP/EWP/QWP/1401/98 “Notes for Guidance on the Investigation of Bioavailability and Bioequivalence”.

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

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

5. EXPERT REPORTS
A satisfactory clinical expert report has been written by an appropriately qualified physician.

6. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPC is consistent with that for the reference product, complies with current guidelines and is satisfactory.

7. PATIENT INFORMATION LEAFLET (PIL)
A full-size colour mock-up of the PIL is supplied. It is consistent with the SPC, complies with current guidelines and is satisfactory.

8. LABELLING
Full-size colour mock-ups of the labelling are supplied. These comply with the current guidelines for a product of this type and are satisfactory.

9. APPLICATION FORM (MAA)
The MAA form is medically satisfactory.

10. DISCUSSION
As the active ingredient, proposed route of administration and dosage are well-established, no new clinical data have been generated for the purpose of this application and none are required. Bibliographic references have been supplied as supporting data.

Bioequivalence to the claimed essentially similar product has been adequately demonstrated.

The requested indications, SPC, PIL and labelling are satisfactory.

The MAA form is satisfactory.

11. MEDICAL CONCLUSION
A marketing authorisation may be granted for this product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Clarithromycin 500mg/vial Lyophilisate 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

As the product is a simple aqueous solution for injection, with an essentially identical quantitative and qualitative composition to those for the reference product, no bioequivalence data were required. The applicant has demonstrated that Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion is a generic product of the reference product Klaricid IV (Abbot Laboratories Limited, UK).

No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied 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 compound.

The risk benefit is, therefore, considered to be positive.

CLARITHROMYCIN 500MG/VIAL LYOPHILISATE FOR SOLUTION FOR INFUSION

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 14th February 2008
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 25th February 2008
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 25th February 2008. There were no requests for further information relating to the clinical dossier.
4	The applicant responded to the MHRA's requests, providing further information on 16th October 2008 for the quality sections.
5	The applications were determined on 30th October 2008

CLARITHROMYCIN 500MG/VIAL LYOPHILISATE FOR SOLUTION FOR INFUSION

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500mg of clarithromycin

3 PHARMACEUTICAL FORM

A white or almost white, Lyophilisate for Solution for Infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion is indicated for the parenteral treatment of infections caused by susceptible organisms in the following conditions:

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

4.2 Posology and method of administration

For intravenous use only. Clarithromycin should not be given as a bolus or as an intramuscular injection. Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion should be administered as an IV infusion over 60 minutes into one of the larger proximal veins using a solution concentration of 2mg/ml. Intravenous therapy may be given for 2 to 5 days after which time the patient should be changed to oral clarithromycin as appropriate. For instructions on appropriate dilution of the product before administration see section 6.6.

Recommended doses are:

Adults:

1.0 gram daily, divided into two 500mg doses diluted as described in Section 6.6.

Children:

Insufficient data exist to recommend a dosing regimen for use in children

Elderly:

The dosing regimen for the elderly does not differ to that recommended for adults.

Renal impairment

The dose of clarithromycin should be reduced to one half of the normal adult recommended dose in renally impaired patients who have a creatinine clearance less than 30ml/minute.

4.3 Contraindications

Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion is contraindicated in patients with a known hypersensitivity to macrolide antibiotic drugs.

Concomitant administration of clarithromycin with any ergot derivatives must be avoided (see section 4.5).

Concomitant administration of cisapride, pimozide and terfenadine is contraindicated with clarithromycin. Elevated plasma levels of cisapride, pimozide, and terfenadine have been reported in patients when these drugs are taken concomitantly with clarithromycin. This may lead to 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.

4.4 Special warnings and precautions for use

As clarithromycin is primarily excreted by the liver and kidneys special care should be taken when administering to patients with impaired hepatic or renal function.
Concomitant use of clarithromycin and colchicine increases the risk of colchicine toxicity, particularly in elderly patients, especially those with renal insufficiency. Deaths have been reported in some of these cases (see section 4.5).

An overgrowth of non-susceptible bacteria or fungi can result following prolonged or repetitive use of clarithromycin. If a super-infection occurs, clarithromycin should be discontinued and appropriate therapy commenced.

4.5 Interaction with other medicinal products and other forms of interaction

Clarithromycin does not interact with oral contraceptives.

As with other macrolide antibiotics, the concomitant use of clarithromycin with drugs metabolised by the cytochrome p450 system may result in elevated serum levels of these other drugs. Examples include cilostazol, methylprednisolone, oral anticoagulants (e.g. warfarin), quinidine, sildenafil, ergot alkaloids, alprazolam, triazolam, midazolam, disopyramide, lovastatin, rifabutin, phenytoin, cyclosporin, vinblastine, valproate and tacrolimus.

Rhahdomyolysis has been reported following co-incident co-administration of clarithromycin and HMG-CoA reductase inhibitors (e.g. lovastatin and simvastatin).

Increased serum theophylline levels have been reported in patients who are receiving clarithromycin and theophylline concomitantly. There is the potential for theophylline toxicity.

Clarithromycin may potentiate the effects of warfarin when administered concomitantly. Prothrombin time should be frequently monitored in these patients.

Monitoring of serum digoxin levels should be considered in patients receiving both clarithromycin and digoxin as the effects of digoxin may be potentiated with concomitant administration.

The use of clarithromycin in patients receiving carbamazepine may cause potentiation of the effects of carbamazepine due to a reduction in the rate of excretion.

The area under the curve (AUC), C_{max} and C_{min} of clarithromycin are all increased when clarithromycin is administered concurrently with ritonavir. However, due to the large therapeutic window of clarithromycin, dose reduction should not be necessary in patients with normal renal function. For renally impaired patients however, the following dose 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.

Torsade de Pointes has been reported following the concurrent use of clarithromycin and quinidine or disopyramide. Levels of these medications should be monitored during clarithromycin therapy.

Co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity. This has been characterised by vasospasm and ischemia of the extremities and other tissues including the central nervous system (see section 4.3).

Concomitant administration of colchicine and clarithromycin may cause an increased exposure to colchicines. Colchicine is a substrate for both CYP3A and the efflux transporter P-glycoprotein (Pgp), both of which are inhibited by clarithromycin and other macrolides. When clarithromycin and colchicine are administered together, patients should be monitored for clinical symptoms of colchicine toxicity (see section 4.4).

4.6 Pregnancy and lactation

Clarithromycin should not be used during pregnancy or lactation unless the benefit is considered to outweigh the risk since the safety of clarithromycin during pregnancy and breast feeding has not been established. Clarithromycin has been found in the milk of lactating animals and in human breast milk.

Although some animal studies have shown clarithromycin to have an embryotoxic effect, this was only observed at doses which were clearly toxic to the mothers.

4.7 Effects on ability to drive and use machines

None reported

4.8 Undesirable effects

The most frequently reported adverse effects in clinical studies included injection site reactions. More specifically, inflammation, tenderness, phlebitis and pain have all been reported at the site of injection. The most common non-infusion related adverse event reported was dysgeusia.

The following adverse effects have been reported following administration of clarithromycin:

Infections and Infestations
Pseudomembranous colitis (severity may range from mild to life-threatening). Oral candidiasis

Blood and lymphatic system disorders
Leukopenia and thrombocytopenia (isolated cases)

Immune system disorders
Hypersensitivity and anaphylactic reactions

Metabolism and nutrition disorders
Hypoglycaemia (rare)

Psychiatric disorders
Psychosis, hallucinations, confusional state, disorientation, depersonalisation, insomnia, abnormal dreams and anxiety

Nervous system disorders
Convulsions (rare), headache, dizziness and dysgeusia.

Eye disorders
Uveitis (rare), mainly in patients treated with concomitant rifabutin. Most events were reversible.

Ear and labyrinth disorders
Deafness (which is usually reversible following discontinuation of therapy), vertigo and tinnitus

Cardiac disorders
Ventricular tachycardia, Torsades de Pointes and QT interval prolongation have rarely been reported.

Gastrointestinal disorders
Pancreatitis (rare), stomatitis, glossitis, tooth and tongue discolouration

Hepato-biliary disorders
Hepatic function abnormal (which is usually reversible but may be severe), hepatitis, cholestasis (with or without jaundice) and abnormal liver function tests. Fatal hepatic failure (rare)

Skin and subcutaneous tissue disorders
Rash, urticaria and angioedema

Musculoskeletal, connective tissue and bone disorders
Arthralgia and myalgia

Renal and urinary disorders
Renal failure, interstitial nephritis and increased blood creatinine (all rare)

General disorders and administration site conditions
Injection site reactions, specifically inflammation, tenderness, phlebitis and pain.

In addition, the following adverse events have been reported following administration of oral clarithromycin:
Nervous system disorders
Paraesthesia

Gastrointestinal disorders
Abdominal pain, diarrhoea, nausea, vomiting and dyspepsia,

Skin and subcutaneous tissue disorders
Stevens-Johnson syndrome and toxic epidermal necrolysis.

There have been reports of colchicine toxicity following concomitant administration of clarithromycin. This has occurred particularly in the elderly some of whom had renal insufficiency. Some such reports have been fatal (See sections 4.4 and 4.5)

4.9 Overdose

There is no experience of overdose with Clarithromycin by the intravenous route. Consequently symptoms accompanying overdose should be treated by supportive measures.

As with other macrolides the serum levels of clarithromycin are not expected to be significantly altered 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

Pharmacotherapeutic group: Macrolide antibacterial for systemic use: ATC J01FA09

Clarithromycin is a semi-synthetic derivative of erythromycin A.

Clarithromycin exerts antibacterial action by binding to the 50s ribosomal subunit thereby inhibiting protein synthesis in susceptible bacteria. Clarithromycin is highly potent against a wide range of aerobic and anaerobic gram-positive and gram-negative organisms and shows excellent *in vitro* activity against standard strains of clinical isolates. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than those of erythromycin from which it is derived.

14-(R)-hydroxyclarithromycin, the first pass metabolite of clarithromycin, has antimicrobial activity with MICs equal to or two-fold higher than the MICs of the parent compound, except for *H. influenzae* where the 14-(R)-hydroxy metabolite is two-fold more active than the parent clarithromycin.

Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion is active against the following micro-organisms *in vitro*:
GRAM-POSITIVE BACTERIA
Staphylococcus aureus (methicillin susceptible); *Streptococcus (Diplococcus) pneumoniae*; *Streptococcus pyogenes* (Group A beta-haemolytic streptococci); Alpha-haemolytic streptococcus (viridans group); *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 also has bactericidal activity against several bacterial strains including; *H influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Moraxella (Branhamella) catarrhalis*, *Neisseria gonorrhoeae*, *Helicobacter pylori* and campylobacter species.

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

5.2 Pharmacokinetic properties
14-hydroxyclarithromycin, the microbiologically active metabolite of clarithromycin, is formed by first pass metabolism as indicated by lower availability of the metabolite following intravenous administration. Blood levels of clarithromycin following IV administration reach in excess of the MIC90s for the common pathogens and the levels of 14-hydroxyclarithromycin exceed the required concentrations for key pathogens (e.g. *H. influenzae*).

Following a single intravenous dose of 500mg over 60 minutes about 33% clarithromycin and 11% of the 14-hydroxyclarithromycin metabolite is excreted in the urine at 24 hours.

The pharmacokinetics of clarithromycin and the 14-hydroxyclarithromycin metabolite are non-linear, with steady state being achieved by day 3 of intravenous dosing.

5.3 Preclinical safety data
There are no relevant preclinical data which are additional to that already in other sections of the SPC

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactobionic acid
Sodium Hydroxide (for pH adjustment)

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

6.3 Shelf life
The unopened shelf-life of Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion is 36 months.

Once reconstituted chemical and physical in-use stability has been demonstrated for 24 hours (at 5ºC to 25ºC) when reconstituted in 10ml of water for injections and for 6 hours (at 25ºC) or 24 hours (at 5ºC) once diluted in 250ml of an appropriate infusion solution.

From a microbiological point of view the product should be used immediately. If not used immediately the 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 2ºC to 8º C unless the reconstitution and dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
No special precautions for storage

6.5 Nature and contents of container
The product is supplied in a 15ml clear Type 1 glass vial sealed with a 20mm grey bromobutyl Type 1 lyophilisation stopper and protected by a 20mm cap that is silver in colour with a red ring on the top surface that incorporates a transparent flip-off plastic top. The product is supplied in packs of 1 vial.

6.6 Special precautions for disposal

Clarithromycin should not be given as a bolus or as an intramuscular injection.

Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion should be administered into one the larger proximal veins as an IV infusion over 60 minutes using a solution concentration of about 2mg/ml. A 2mg/ml solution may be obtained by reconstituting the product in 10ml of water for injections. Once dissolution is complete, the 10ml solution must be added to 250ml of a suitable infusion solution/diluent (see below) in order to obtain a 2mg/ml solution.

Recommended infusion solutions/diluents are;

- 5% Dextrose in Lactated Ringers solution
- 5% Dextrose
- Lactated Ringers solution
- 5% Dextrose in 0.3% Sodium chloride
- Normosol-M in 5% Dextrose
- Normosol-R in 5% dextrose
- 5% Dextrose in 0.45% Sodium chloride
- 0.9% Sodium chloride.

Compatibility with other intravenous additives has not been established.

Diluents containing preservatives or inorganic salts should not be used.

Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Britannia Pharmaceuticals Limited
41 – 51 Brighton Road
Redhill
Surrey
RH1 6YS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04483/0063

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/11/2008

10 DATE OF REVISION OF THE TEXT

03/11/2008

11 DOSIMETRY (IF APPLICABLE)

Not applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not applicable

PATIENT INFORMATION

Clarithromycin 500mg/vial

Lyophilisate for Solution for Infusion*

**For easier reading the product is called "Clarithromycin 500mg/vial" in the rest of this leaflet.*

Please read all of this leaflet carefully before you receive this medicine

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

In this leaflet:

1. What Clarithromycin 500mg/vial is and what it is used for

Clarithromycin 500mg/vial contains clarithromycin. Clarithromycin belongs to a group of drugs called macrolides and is an antibiotic which stops the growth of many types of "bugs" that cause infections.

Clarithromycin 500mg/vial may be used to treat:

- Chest infections such as bronchitis and pneumonia.
- Throat and sinus infections.
- Skin and soft tissue infections.

2. Before you are given Clarithromycin 500mg/vial

Do not take Clarithromycin 500mg/vial if you are;

- Allergic to clarithromycin or other macrolide antibiotics such as erythromycin or azithromycin, or if you are allergic to any of the other ingredients listed in section 6, Further Information.
- Taking any medicines for headaches containing ergotamine or dihydroergotamine, since taking these medicines with Clarithromycin may cause your blood vessels to narrow.
- Taking any medicines containing;
  - pimozide (a drug for psychiatric conditions).
  - cisapride (a drug for stomach disorders).
  - terfenadine or astemizole (drugs for hay fever or allergy).

Taking these medicines with Clarithromycin 500mg/vial can sometimes cause serious changes in the rhythm of your heart.

Take special care with Clarithromycin 500mg/vial and tell your doctor if;

- You have any liver or kidney problems.
- You have been given Clarithromycin 500mg/vial for a long period of time or on a regular basis, as this may allow resistant "bugs" to grow.
- You are taking colchicine, a drug used to treat gout.

Taking other medicines:

You should tell your doctor or nurse if you are taking, or have recently taken, any of the following medicines as they may interact with Clarithromycin 500mg/vial:

- Digoxin, quinidine or disopyramide (drugs for the heart).
- Warfarin or other drugs to thin the blood.
- Carbamazepine, valproate or phenytoin (drugs for epilepsy).
- Theophylline (a drug to help breathing).
- Triazolam, alprazolam or midazolam (drugs to help you sleep).
- Cilostazol (drugs for poor circulation).
- Simvastatin or lovastatin (drugs for high cholesterol).
- Methylprednisolone (a corticosteroid).
- Vinblastine (a drug for the treatment of cancer).
- Sildenafil (a drug for impotence).
- Cyclosporin (a drug that affects your immune system).
- Zidovudine (an anti-viral drug).
- Rifabutin (a drug for treatment of some infections).
- Tacrolimus (a drug taken to prevent rejection of organ transplants).
- Colchicine (a drug for gout).
- Ritonavir (a drug for the treatment of HIV).

Clarithromycin 500mg/vial does not interfere with the effect of oral contraceptives.

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

Pregnancy and breast-feeding:

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

Driving and using machines:

Clarithromycin 500mg/vial has no known effects on the ability to drive or operate machines.

3. How Clarithromycin 500mg/vial is given

Clarithromycin 500mg/vial will be prepared by your doctor or nurse. It will be given to you by infusion into one of your veins (like a blood transfusion) over a period of at least one hour.

Adults and the elderly:
The usual dose of Clarithromycin 500mg/vial is 500 mg (1 vial) taken twice a day for a period of 2 to 5 days. Your doctor or nurse will work out the correct dose for you.

If you suffer from weak or damaged kidneys then your dose should be reduced to half of the normal adult recommended dose.

Children:
There is no information on the use of Clarithromycin in children.

Turn over

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TECHNICAL INFORMATION

Clarithromycin 500mg/vial

Lyophilisate for Solution for Infusion

Recommended Administration

Clarithromycin 500mg/vial 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 as an intramuscular injection

Recommended Preparation and Storage

Do not use after the expiry date which is stated on the vial and carton. The expiry date refers to the last day of that month.

This product should be prepared as follows.

STEP 1

Add 10ml of sterile water for injections into the vial and shake until fully dissolved.

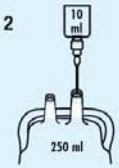
Storage

Chemical and physical in-use stability has been demonstrated for 24 hours (at 5°C to 25°C) - however from a microbiological point of view the product should be used immediately.

DO NOT USE

- Diluents containing preservatives.
- Diluents containing inorganic salts.

STEP 2



Add 10ml solution from Step 1 to 250ml of a suitable infusion diluent (see above) to provide a 2mg/ml solution.

Storage

Chemical and physical in-use stability has been demonstrated for 6 hours (at 25°C) or 24 hours (at 5°C) - however from a microbiological point of view the product should be used immediately.

DO NOT USE

- Solution strengths greater then 2mg/ml (2%).
- Rapid infusion rates (< 60 minutes).

Failure to observe these precautions may result in pain along the vein.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Recommended Diluents

Recommended infusion solutions/diluents are;

5% Dextrose in Lactated Ringers solution, 5% Dextrose, Lactated Ringers solution, 5% Dextrose in 0.3% Sodium chloride, Normosol-M in 5% Dextrose, Normosol-R in 5% dextrose, 5% Dextrose in 0.45% Sodium chloride or 0.9% Sodium chloride. Compatibility with other intravenous additives has not been established.

Do not use diluents containing preservatives or inorganic salts.

Other information

This medicinal product contains less than 1 mmol sodium (23mg) per 500mg, i.e. it is essentially 'sodium free'.

Full prescribing information is available on the Summary of Product Characteristics.

Continued from other side

4. Possible side effects

Like all medicines, Clarithromycin 500mg/vial can cause side effects, although not everybody gets them.

All medicines can cause allergic reactions although serious allergic reactions are very rare. If you get any of the following symptoms after receiving Clarithromycin 500mg/vial, you should contact your doctor immediately;

- **Any sudden wheeziness, difficulty in breathing, swelling of the face, eyelids, lips or throat.**
- **Peeling and blistering of the skin, mouth and lips.**

The most common side effects with Clarithromycin 500mg/vial are:

- Inflammation, pain or tenderness at the point of infusion.
- Abnormal taste.

The following side effects have also been reported:

- itchy rash
- headache
- dizziness
- changes in taste
- changes in smell
- loss of hearing
- seeing or hearing things
- confusion
- difficulty sleeping
- abnormal dreams
- loss of reality
- anxiety
- feeling sick
- vomiting
- stomach pain
- indigestion
- diarrhoea
- inflammation of mouth or tongue
- sore mouth
- 'thrush' in mouth
- tooth or tongue discolouration
- 'pins and needles'
- joint pain
- muscle pain
- 'ringing in ears'
- hearing loss (which usually gets better when treatment stops)
- liver problems
- yellowing of skin and/or whites of eyes

Rarely, the following may also occur;

- changes in heart rhythm
- inflammation of pancreas
- Severe or prolonged diarrhoea
- convulsions
- Inflammation of eye, especially if also taking rifabutin (reversible)
- kidney problems
- kidney failure
- liver failure resulting in death

In addition a blood test may show that you have;

- low levels of white cells that fight infection
- low levels of cells that help blood clot (which may result in bruising)
- a low blood sugar level
- abnormal liver tests (which usually return to normal when treatment stops)
- abnormal kidney tests

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

5. How Clarithromycin 500mg/vial is stored

The hospital will ensure that Clarithromycin 500mg/vial is stored correctly and that it is not used after the expiry date stated on the vial label and carton.

6. Further information

What Clarithromycin 500mg/vial contains:

Each vial of Clarithromycin 500mg/vial contains;

Active ingredient:
500mg of sterile clarithromycin as the active ingredient, which provides 2mg/ml of clarithromycin when reconstituted as recommended.

Other ingredients:
Lactobionic acid and sodium hydroxide.

What Clarithromycin 500mg/vial looks like:

Clarithromycin 500mg/vial Lyophilisate for Solution for Infusion is a white/almost white sterile freeze-dried powder in a glass vial.

Marketing Authorisation Holder and Manufacturer:

Britannia Pharmaceuticals Ltd.
41 – 51 Brighton Road
Redhill, Surrey, RH1 6YS.
United Kingdom.

Product licence reference numbers:

PL 04483/0063

If you have any questions about your treatment with Clarithromycin 500mg/vial which are not answered by this leaflet, please ask your doctor or nurse.

This leaflet was last approved in:

{MM/YYYY}.

UK001

Britannia
Pharmaceuticals Limited

Clarithromycin 500mg

Lyophilisate for Solution for Infusion

Britannia Pharmaceuticals Limited

For intravenous use only, as a 250ml infusion.
Each vial contains 500mg of sterile clarithromycin, which provides 2mg/ml of clarithromycin when reconstituted as recommended. **Consult the package leaflet for information on reconstitution.**
The product also contains lactobionic acid and sodium hydroxide.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Britannia Pharmaceuticals Ltd., Redhill, Surrey. RH1 6YS.
POM PL04483/0063 UK001 RFI1

Batch number:

Expiry date:

Pharma code area