Public Assessment Report

Clarithromycin 500mg/vial Powder for Infusion

Clarithromycin

PL 10622/0260

Pliva Pharma Ltd

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Lay Summary

The MHRA granted Pliva Pharma Ltd a marketing authorisation (licence) for the medicinal product Clarithromycin 500mg/vial Powder for Infusion (PL 10622/0260) on 13th December 2007. The active ingredient is clarithromycin which is an antibacterial medicine used to treat respiratory tract infections and infections of the skin and soft tissue.

Clarithromycin 500mg/vial Powder for Infusion was demonstrated to be the same as the reference product Klaricid 500mg/vial Powder for Solution for Injection. The product is a prescription only medicine.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Clarithromycin 500mg/vial Powder for Infusion outweigh the risks, hence Marketing Authorisations have been granted.

Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal product Clarithromycin 500mg/vial Powder for Infusion (PL 10622/0260) on 13th December 2007.

Clarithromycin 500mg/vial Powder for Infusion was demonstrated to be a generic medical product of Klaricid 500mg/vial Powder for Solution for Injection (PL 00037/0251), granted 22/9/1993 to Abbott Laboratories Ltd.

The product contains the active ingredient clarithromycin. 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 suppressing protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms.

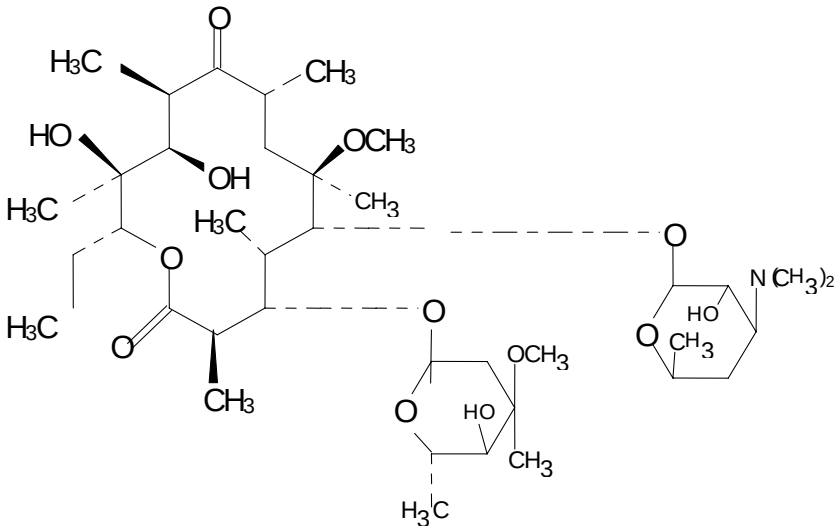
Clarithromycin 500mg/vial Powder for Infusion is indicated whenever parenteral therapy is required for treatment of infections caused by susceptible organisms in the following conditions:

- 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.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Structure



Mol formula $C_{38}H_{69}NO_{13}$ Molecular Mass 748

Clarithromycin is (3R, 4S, 5S, 6R, 7R, 9R, 11R, 12R, 13S, 14R)-4-[(2,6-dicleoxy-3-C-methyl-3-0-methyl-x-L-nbo-hexopyranosyl)oxy]-14-ethyl-12, 13-dihydroxy-7-methoxy-3, 5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2, 10-dione(6-0-methylerythromycin A).

Clarithromycin is a white or almost white powder.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Clarithromycin stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 24 months, with no specific storage instructions.

DRUG PRODUCT

Other ingredients

The drug product contains lactobionic acid and sodium hydroxide. Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their respective European Pharmacopoeial monograph. Lactobionic acid is obtained synthetically from calcium lactobionate, which is obtained from lactose derived from the milk of healthy cows. It is declared that there are no other materials of animal or human origin.

Impurity Profile

The impurity profile of Clarithromycin 500mg/vial Powder for Infusion was found to be similar to Klaricid 500mg/vial Powder for Solution for Injection.

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. Satisfactory process validation has been carried out.

Finished product specification

The finished product specification is 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. 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 drug product is contained in a glass vial with a chlorobutyl rubber seal. The glass vials and rubber stoppers comply with the Ph Eur monograph specifications for glass containers and rubber seals respectively for parenteral preparations.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. There are no special storage conditions. The product should be used within 8 hours of reconstitution.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRE-CLINICAL ASSESSMENT

No pre-clinical data were presented with this application and none were required.

MEDICAL ASSESSMENT

Pharmacodynamic properties

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 suppressing protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms.

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_{90}s 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.

Clinical Expert Report

A satisfactory clinical expert report by a suitably qualified expert was provided.

Efficacy

The efficacy profile of clarithromycin is well established. No new efficacy data are required for theses applications.

Safety

The safety profile of clarithromycin is well established. No new efficacy data are required for theses applications.

Summary of Product Characteristics

The Summary of Product Characteristics can be found on page 11 of this report and was satisfactory.

Patient Information Leaflet

The Patient information leaflet is satisfactory.

Conclusion

A marketing authorisation was granted.

Overall Conclusion and Risk/Benefit Analysis

Quality

The important quality characteristics of Clarithromycin 500mg/vial Powder 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.

Pre-Clinical

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

Clinical

No bioequivalence study was required for this type of product. No new or unexpected safety concerns arise from these applications. The SPC, PIL and labelling are satisfactory and consistent with the reference product.

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 13th December 2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 20th December 2004.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 12th May 2005, 8th June 2005 and 17th January 2007.
4	The applicant provided further information in regard to the quality assessment on 7th June 2005, April 2006 and 5th October 2007.
5	The application was determined on 13th December 2007.

Steps Taken after Assessment

None

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 500mg/vial Powder for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clarithromycin 500mg/vial. Each vial contains 500mg clarithromycin.
When reconstituted the solution strength is 2mg/ml.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Lyophilised powder for reconstitution to give a solution for IV administration. The description of the product is a white crystalline powder. The appearance of the product after reconstitution is a clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarithromycin 500mg/vial Powder 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 of Clarithromycin 500mg/vial Powder for Infusion is 1.0 gram daily, divided into two 500mg doses, appropriately diluted as described below.
Children: At present, there are insufficient data to recommend a dosage regimen for routine use in children.
Elderly: As for adults.
Renal Impairment: Dosage adjustments are not usually required except in patients with severe renal impairment (creatine clearance <30ml/min). If adjustment is necessary the total daily dosage should be reduced to one half of the normal recommended dose.
Recommended administration:

Clarithromycin 500mg/vial Powder 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.
The method of dilution is:
Step 1. Reconstitute with 10ml Water for Injection.
Step 2. Dilute solution from Step 1 to 250ml with recommended diluents to form a solution of approximately 2mg/ml.
The recommended diluents are:
0.9% sodium chloride solution or 5.0% glucose solutions or Ringer lactate solution.
The appearance of the product after reconstitution is a clear solution.
Both dilution steps must be followed before administration.

4.3 Contraindications

Clarithromycin 500mg/vial Powder for Infusion is contra-indicated in patients with known hypersensitivity to clarithromycin, to any other macrolide antibiotic drugs.
Clarithromycin 500mg/vial Powder 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

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.
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).

4.5 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. cilostazol, methylprednisolone, oral anticoagulants (eg warfarin), quinidine, sildenafil, ergot alkaloids, alprazolam, triazolam, midazolam, disopyramide, lovastatin, rifabutin, phenytoin, cyclosporin, vinblastine, valproate 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 coadministered 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 have been reported. There have been reports of Stevens-Johnson syndrome/ toxic epidermal necrolysis with orally administered clarithromycin.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 clarithromcyin.

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

ATC Code: J01FA09

General properties

Mode of action

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 suppressing protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-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 antimicrobial activity. The MICs of this metabolite are equal 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/vial Powder for Solution for Infusion 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_{90}s 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.
Clarithromycin 500 mg/vial Powder for Solution for Infusion does not contain tartrazine or other azo dyes, lactose or gluten.

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
Sodium hydroxide

6.2 Incompatibilities
None known. However, Clarithromycin 500mg/vial Powder for Infusion should only be diluted with the diluents recommended.

6.3 Shelf life
24 months unopened. This medicinal product does not require any special storage conditions.
Chemical and physical in-use stability has been demonstrated for 8 hours at room temperature and 24 hours at 2 to 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would not normally 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
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
20ml vial (Glass Type I, Ph.Eur 3.2.1) with a cholorobutyl stopper with an aluminium and plastic flip-off cap. Vials are packed in units of 1, 4 and 6. Pack size 500mg.

6.6 Special precautions for disposal

Special precautions for handling

Clarithromycin 500mg/vial Powder 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.
The method of dilution is:
Step 1. Reconstitute with 10ml Water for Injection.
Step 2. Dilute solution from Step 1 to 250ml with recommended diluents to form a solution of approximately 2mg/ml.
The recommended diluents are:
0.9% sodium chloride solution or 5.0% glucose solutions or Ringer lactate solution
Both dilution steps must be followed before administration.

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

PLIVA Pharma Ltd
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0260

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/12/2007

10 DATE OF REVISION OF THE TEXT

13/12/2007

Labels and Leaflet

PATIENT INFORMATION LEAFLET

Clarithromycin 500mg/vial Powder for Infusion

Read this entire leaflet carefully before the doctor or nurse starts to give you this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

This leaflet contains the following information:

The name of your medicine is Clarithromycin 500mg/vial Powder for Infusion (Clarithromycin Infusion).
Each vial contains 500mg of the active ingredient Clarithromycin. When made up with Water for Injections and a larger volume of diluent for infusion, each milliliter of solution contains 2mg of clarithromycin. The other ingredients are lactobionic acid and sodium hydroxide.

Marketing Authorisation Holder:
PLIVA Pharma Ltd, Vision House, Bedford Road, Petersfield, Hampshire, GU32 3QB, United Kingdom.

Manufacturer:
Reig Jofré, S.A., Gran Capitá, 10 08970 Sant Juan Despí (Barcelona), Spain.

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

Clarithromycin is one of a group of antibiotics called macrolides. These antibiotics are used to treat infections due to sensitive bacteria, including:

- chest infections e.g. bronchitis or pneumonia;
- nose or throat infections e.g. sinusitis;
- skin or soft tissue infections.

2 Information to read BEFORE you are given Clarithromycin 500mg/vial Powder for Infusion.

Please take the time to read the following information carefully as this may stop you from being able to be given Clarithromycin Infusion.

When should you NOT be given Clarithromycin 500mg/vial Powder for Infusion?

Please ask yourself the following questions:

- Have you ever taken a medicine containing Clarithromycin, another macrolide or azolide antibiotic (e.g. erythromycin, azithromycin) or lactobionic acid and had an unusual or allergic reaction e.g. rash, swelling of the face, lips, hands or feet or had breathing difficulties?
- Are you taking ergot derivatives e.g. ergotamine or dihydroergotamine (medicines used for migraines or reducing blood flow)?
- Are you taking cisapride, a medicine used to treat heartburn?
- Are you taking pimozide, a medicine used to treat schizophrenia and other mental illnesses?
- Are you taking terfenadine, a medicine for allergies such as hayfever?
- Are you taking astemizole, a medicine used to treat allergic reactions?
- Are you taking colchicine, a medicine used to treat gout or other kidney problems
- Are you pregnant or could you be pregnant?
- Are you breastfeeding?

If the answer to any of these questions is YES, tell the doctor or nurse who will be giving you this medicine, as soon as possible and before the infusion is given to you. Your doctor will then decide whether you should receive Clarithromycin Infusion.

When should you take special care while being given Clarithromycin 500mg/vial Powder for Infusion?

Ask yourself the following questions:

- Do you suffer from liver problems?
- Do you suffer from kidney problems?
- Are you having a series of clarithromycin infusions and have suffered from other types of infection during this course e.g. thrush?
- Are you taking triazolam, alprazolam or midazolam (sedatives), lovastatin, simvastatin, atorvastatin (to reduce your cholesterol), rifabutin (for treatment of some infections), ciclosporin (used following organ transplants, for skin conditions, or for rheumatoid arthritis), tacrolimus (used after organ transplants), valproate (for epilepsy), methylprednisolone (a corticosteroid), vinblastine (for cancer therapy), cilostazol (for walking difficulties), sildenafil (erectile dysfunction)? Clarithromycin may cause an increase in the level of these medicines in your blood.
- Are you taking quinidine or disopyramide (for heart problems)?
- Are you taking phenytoin, phenobarbital or carbamazepine (for epilepsy), rifampicin (an antibiotic), St John's wort (a herbal medicine) or efavirenz (for HIV)? These medicines may reduce the level of Clarithromycin in your blood.
- Are you taking theophylline (for breathing problems)? Clarithromycin may cause raised blood levels and possible side-effects from this medicine.
- Are you taking warfarin (to thin the blood) or digoxin (used to treat heart failure)? Clarithromycin may increase the effects of these medicines. Your doctor may choose to do more frequent blood tests to check the activity of warfarin or the blood levels of digoxin.
- Are you taking zidovudine (an HIV treatment)? Clarithromycin may reduce the blood levels of zidovudine and should therefore be taken at least 1-2 hours before or after zidovudine.
- Are you taking ritonavir (an HIV treatment)? Ritonavir may increase the blood levels of clarithromycin which can cause problems if you have kidney problems. In this case your doctor may choose to reduce your dose of clarithromycin.
- Do you have heart disease, other problems with your heart or blood vessels, slow or irregular heart beat or heart failure or have a history of these conditions?

If the answer to any of these questions is YES and you have not already discussed this with your doctor or nurse, you should do so as soon as possible and before being given the infusion.

If you are not sure whether another medicine you are taking may be one of the types listed above, check with your doctor or nurse. Please tell your doctor or nurse if you are taking, or have recently taken any other medicine including those that you have bought with out a prescription.

Clarithromycin does not interact with oral contraceptives (the pill).

Pregnancy and breastfeeding

You should not take any medicine without first discussing it with your doctor if you are pregnant or breastfeeding.

Effects on your ability to drive and use machines

This infusion should not affect your ability to drive or use machines.

3 How Clarithromycin 500mg/vial Powder for Infusion is given

Clarithromycin Infusion will be diluted using certain liquids and be given as an infusion (a 'drip') into a vein over an hour. You should be given a leaflet about the liquid used. If you require further information, ask the doctor or nurse who will be giving or who has given you the medicine.

Adults and Elderly

The usual dose for adults is 2 infusions of 500mg a day. This gives a total dose per day of 1g.

Patients with kidney problems

If you have severe kidney problems your doctor may decide to reduce your dose.

Children

Clarithromycin Infusion is not recommended for use in children

Overdose

Your dose will be carefully calculated by the doctors, so overdose is unlikely. If you think you have been given too much Clarithromycin Infusion you should talk to your nurse or doctor.

4 Possible side effects.

Like all medicines, Clarithromycin Infusion may have side effects.

As with all antibiotics some people may experience an allergy to this medicine. If you experience any of the following symptoms tell your doctor or nurse immediately:

- Swelling of the hands, feet, ankles, face, lips, mouth or throat.
- Problems with swallowing or breathing.

The most common side effect is around the injection site in the form of swelling, soreness pain and inflammation of the vein. The most common side effect not related to having an infusion is a changed sense of taste. This may include a changed sense of smell.

The following are common side effects. They may happen in less than 1 in every 10 people using Clarithromycin Infusion:

- Yeast infections of the mouth (thrush).
- Headache, a metallic or bitter taste in the mouth, altered sense of smell.
- Feeling or being sick, diarrhoea, lower stomach pain (abdomen), heartburn, inflammation of your tongue, lips, cheeks or gums, discolouration of the tongue and teeth (reversible).
- Changes in the results of some blood tests e.g. BUN – blood urea nitrogen.

The following are uncommon side effects. They may happen in less than 1 in every 100 people using Clarithromycin Infusion:

- Decreased levels of white blood cells which may reduce your ability to fight infections.
- Allergic reactions including skin rashes, itching and swelling of your hands or feet. Severe allergic reactions which may include swelling of the face, lips, hands or feet, or breathing difficulties.
- Liver problems, increased levels of liver enzymes in the blood, problems with bile production and jaundice (yellowing of the skin and whites of the eyes).
- Pain in the joints or muscles.
- Changes in the results of some blood tests e.g. clotting time and increased levels of creatinine (an enzyme).

The following is a rare side effect. This may happen in less than 1 in every 1000 people using Clarithromycin Infusion:

- Tinnitus (ringing in the ears).

Inflammation of the eye has also been reported in patients having Clarithromycin. This was mainly seen in people who were also taking rifabutin. This side-effect got better in most patients after they had finished having Clarithromycin.

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skin eruptions and angioedema to anaphylaxis have been reported. There have been reports of Stevens-Johnson syndrome/ toxic epidermal necrolysis with orally administered clarithromycin. 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 gastrointestinal 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 hypocarnia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: J01FA09

General properties

Mode of action

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 suppressing protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-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 antimicrobial activity. The MICs of this metabolite are equal 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/vial Powder for Solution for Infusion 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 Bacteroides 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, Moraxella (Branhamella) 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 MICROs 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.

Clarithromycin 500 mg/vial Powder for Solution for Infusion does not contain tartrazine or other azo dyes, lactose or gluten

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. Sodium hydroxide.

6.2 Incompatibilities

None known. However, Clarithromycin 500mg/vial Powder for Infusion should only be diluted with the diluents recommended.

6.3 Shelf life

24 months unopened. This medicinal product does not require any special storage conditions.

Chemical and physical in-use stability has been demonstrated for 8 hours at room temperature and 24 hours at 2 to 8° C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would not normally 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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

20ml vial (Glass Type I, Ph.Eur 3.2.1) with a chlorobutyl stopper with an aluminium and plastic flip-off cap. Vials are packed in units of 1, 4 and 6. Pack size: 500mg.

6.6 Special precautions for disposal and other handling

Clarithromycin 500 mg/vial Powder 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.

The method of dilution is:

Step 1. Reconstitute with 10ml Water for Injection.

Step 2. Dilute solution from Step 1 to 250ml with recommended diluents to form a solution of approximately 2mg/ml.

The recommended diluents are:

0.9% sodium chloride solution or 5.0% glucose solutions or Ringer lactate solution.

Both dilution steps must be followed before administration.

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

7 Marketing Authorisation Holder

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

8 Marketing Authorisation Number(S)

PL 10622/0260

9 Date of first Authorisation/ Renewal of the Authorisation

10 Date of revision of the text

PLIVA

SUMMARY OF PRODUCT CHARACTERISTICS

Clarithromycin 500mg/vial Powder for Infusion

Product Summary

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 500mg/vial Powder for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clarithromycin 500mg/vial. Each vial contains 500mg clarithromycin. When reconstituted the solution strength is 2mg/ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lyophilised powder for reconstitution to give a solution for IV administration.

The description of the product is a white crystalline powder. The appearance of the product after reconstitution is a clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarithromycin 500mg/vial Powder 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 of Clarithromycin 500mg/vial Powder for Infusion is 1G gram daily, divided into two 500mg doses, appropriately diluted as described below.

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

Elderly: As for adults.

Renal Impairment: Dosage adjustments are not usually required except in patients with severe renal impairment (creatine clearances <30ml/min). If adjustment is necessary the total daily dosage should be reduced to one half of the normal recommended dose.

Recommended administration:

Clarithromycin 500mg/vial Powder 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.

The method of dilution is:

Step 1. Reconstitute with 10ml Water for Injection.

Step 2. Dilute solution from Step 1 to 250ml with recommended diluents to form a solution of approximately 2mg/ml.

The recommended diluents are:

0.9% sodium chloride solution or 5.0% glucose solutions or Ringer lactate solution.

The appearance of the product after reconstitution is a clear solution.

Both dilution steps must be followed before administration.

4.3 Contraindications

Clarithromycin 500mg/vial Powder for Infusion is contra-indicated in patients with known hypersensitivity to clarithromycin, to any other macrolide antibiotic drugs.

Clarithromycin 500mg/vial Powder 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.

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.

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)

4.5 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. colchicine, methylprednisolone, oral anticoagulants (eg warfarin), quinidine, sildenafil, ergot alkaloids, alprazolam, triazolam, midazolam, disopyramide, lovastatin, rifabutin, phenytoin, cyclosporin, vinblastine, valproate and tacrolimus) may be associated with elevations in serum levels of these other drugs.

Rifabdomycin, 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. Itraconazole 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 characterised 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 pseudomembranous colitis. Stomatitis, glossitis and oral moniliasis have been reported. Other side-effects include headache, teeth and tongue discolouration, arthralgia, myalgia and allergic reactions ranging from urticaria, mild


Batch:
Expiry:
FOR INTRAVENOUS USE ONLY
Each vial contains 500mg clarithromycin.
To be administered as directed by a doctor.
• Dilution:
1. Reconstitute with 10ml Water for Injection.
2. Dilute solution from step 1 to 250ml with recommended diluent to form a solution of approximately 2mg/ml.
See leaflet for further details.
Both dilution steps must be followed before administration.
For single use only. Any unused solution and the vial should be adequately disposed of, in accordance with local requirements.
Chemical and physical in-use stability has been demonstrated for 8 hours at room temperature and 24 hours at 2 to 8°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.
• Dilute in recommended solutions only.
• Other ingredients are lactobionic acid and sodium hydroxide.
• For further information please read the enclosed leaflet.
• No special storage conditions prior to reconstitution.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Clarithromycin
500mg/vial
Powder for Infusion
1 vial
Powder for solution for intravenous infusion
PLIVA
Clarithromycin
500mg/vial
Powder for Infusion
Powder for solution for intravenous infusion
1 vial
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