Clarithromycin 500 mg Powder for Solution for Infusion

PL 04515/0163

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Hospira UK Limited a Marketing Authorisation (licence) for the medicinal product Clarithromycin 500 mg Powder for Solution for Infusion (PL 04515/0163) on 23 November 2011. This is a prescription-only medicine (POM).

Clarithromycin 500 mg Powder for Solution for Infusion contains the active ingredient clarithromycin, which belongs to a group of medicines called ‘macrolide antibiotics’. Antibiotics stop the growth of bacteria which cause infections. Clarithromycin 500 mg Powder for Solution for Infusion is used when an intravenous antibiotic is required to treat severe infections. It is used to treat chest infections such as bronchitis or pneumonia, throat or sinus infections, and skin or soft tissue infections.

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

Based on the data submitted by Hospira UK Limited, Clarithromycin 500 mg Powder for Solution for Infusion was considered to be a generic version of the reference product, Klaricid IV 500 mg/vial Powder for Solution for Injection (PL 00037/0251, Abbott Laboratories Limited).

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

**PL 04515/0163**

## SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Hospira UK Limited a Marketing Authorisation for the medicinal product, Clarithromycin 500 mg Powder for Solution for Infusion (PL 04515/0163) on 23 November 2011. The product is a prescription-only medicine (POM).

This is a generic application for Clarithromycin 500 mg Powder for Solution for Infusion, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The application refers to the UK product, Klaricid IV 500 mg/vial Powder for Solution for Injection (PL 00037/0251), authorised to Abbott Laboratories Limited on 22 September 1993. The reference product has been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

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

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

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Clarithromycin is a macrolide antibiotic (ATC code – J01FA09) and a semi-synthetic derivative of erythromycin. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses 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-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal to or two-fold higher than the MICs of the parent compound, except for *H. influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Resistance mechanisms against macrolide antibiotics include alteration of the target site of the antibiotic, or are based on the modification and/or active efflux of the antibiotic.

The medicinal product is presented as a white to off-white powder or lyophilised plug for solution for infusion. The powder should be reconstituted in sterile water and is then compatible for dilution with a variety of solutions for infusion, as detailed in Section 6.6 of the Summary of Product Characteristics (SmPC). This medicine is not for self-administration; it will be administered to the patient by a healthcare professional.
No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that this is a generic application cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

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

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a detailed Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

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

ACTIVE SUBSTANCE

Clarithromycin

Nomenclature:

INN: Clarithromycin

Structure:

![Chemical Structure of Clarithromycin]

Molecular formula: $C_{38}H_{69}NO_{13}$
Molecular weight: 748 g/mol
CAS No: 81103-11-9
Physical form: A white or almost white crystalline powder
Solubility: Practically insoluble in water, soluble in acetone and in methylene chloride, slightly soluble in methanol

The active substance, clarithromycin, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of clarithromycin are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of clarithromycin for inclusion in this medicinal product.
MEDICINAL PRODUCT

Description & Composition

Clarithromycin 500 mg Powder for Solution for Infusion is presented as a white to off-white powder or lyophilised plug for solution for infusion. The medicinal product is supplied in a glass vial containing 500 mg clarithromycin. The powder should be reconstituted with sterile water and then diluted with one of the intravenous fluids listed in section 6.6 of the SmPC. At the time of administration, the reconstituted and diluted solution for infusion should be at a concentration of 2 mg/ml.

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

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

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The aim was to develop a stable, generic medicinal product, pharmaceutically equivalent to the reference product, Klaricid IV 500 mg/vial Powder for Solution for Injection (Abbott Laboratories Limited).

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted and the results were satisfactory. A commitment has been made by the MAH that full process validation will be conducted on commercial scale batches in accordance with the process validation protocol.

Finished product specification

Finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

Clarithromycin 500 mg Powder for Solution for Infusion is supplied in packs of 1, 4 or 6x 20 ml, type I glass vials complete with bromobutyl stoppers and aluminium
seals. The vials are packaged, with the product information leaflet, into cardboard outer cartons.

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

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support a shelf-life of 2 years for the unopened vial, with storage instructions ‘Store the vial in the outer carton’.

After reconstitution with 10 ml of water for injections, chemical and physical in-use stability has been demonstrated for 24 hours at 5°C - 25°C. After dilution in 250 ml of a recommended diluent (see SmPC section 6.6), chemical and physical stability has been demonstrated for 6 hours at 25°C or 24 hours at 5°C.

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

Chemical and physical compatibility of Clarithromycin 500 mg Powder for Solution for Infusion have been demonstrated with the intravenous fluids stated in section 6.6 of the SmPC, which also provides information regarding disposal of the product.

**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information:**

The approved Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The PIL user-testing report has been evaluated and is accepted. It supports the readability of the package leaflet.

**Conclusion**

The proposed product has been shown to be a generic version of the reference product, Klaricid IV 500 mg/vial Powder for Solution for Injection (Abbott Laboratories Limited), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the EU for over 10 years.

The quality grounds for this application are considered adequate. There are no objections to approval of Clarithromycin 500 mg Powder for Solution for Infusion from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

This generic application, submitted under Article 10(1) of Directive 2001/83/EC, as amended, is for Clarithromycin 500 mg Powder for Solution for Infusion, claiming to be a generic medicinal version of the UK reference product, Klaricid IV 500 mg/vial Powder for Solution for Injection (PL 00037/0251, Abbott Laboratories Limited).

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

A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

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

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

**CLINICAL BACKGROUND**

Clarithromycin belongs to the macrolide antibiotics; it is a derivative of erythromycin with slightly greater activity than the parent compound and higher tissue concentrations.

**INDICATIONS**

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

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

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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

**POSOLOGY AND METHOD OF ADMINISTRATION**

The recommended does is 1 g/day, divided into two 500 mg doses, and should be adjusted if creatinine clearance is less than 30ml/min.

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

**TOXICOLOGY**

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

**CLINICAL PHARMACOLOGY**

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

**CLINICAL EFFICACY**

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

Clarithromycin 500 mg Powder for Solution for Infusion is to be administered as an intravenous solution and contains the same active substance, in the same concentration, as the UK reference product, Klaricid IV 500 mg/vial Powder for
Solution for Injection (Abbott Laboratories Limited). Thus, in accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), Section 5.1.6 Parenteral solutions, the applicant is not required to submit a bioequivalence study.

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

Clinical overview
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPC is consistent with that for the reference product and is acceptable.

Patient Information Leaflet (PIL)
The final PIL is in line with the approved SmPC and is satisfactory.

Labelling
The labelling is satisfactory.

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

QUALITY
The important quality characteristics of Clarithromycin 500 mg Powder for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

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

The applicant’s Clarithromycin 500 mg Powder for Solution for Infusion has been demonstrated to be a generic version of the UK reference product, Klaricid IV 500 mg/vial Powder for Solution for Injection (Abbott Laboratories Limited).

No new or unexpected safety concerns arise from this application.

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

The final PIL is in line with the SmPC and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Clarithromycin 500 mg Powder for Solution for Infusion and the reference product, Klaricid IV 500 mg/vial Powder for Solution for Injection (Abbott Laboratories Limited), are interchangeable. Extensive clinical experience with clarithromycin is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Clarithromycin 500 mg Powder for Solution for Infusion

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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on 10 August 2005.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 12 August 2005.

3 Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 27 January 2006, 09 March 2007, 18 July 2007 and 03 June 2011; and further information relating to the quality dossier on 01 June 2011.

4 The applicant responded to the MHRA’s requests, providing further information for the clinical sections on 18 August 2006, 05 June 2007, 06 August 2010 and 05 October 2011; and further information for the quality sections on 05 October 2011.

5 The application was determined on 23 November 2011.
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STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Clarithromycin 500 mg/vial
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Powder for solution for infusion (Powder for Infusion)
Vials containing a white to off white powder or lyophilised plug.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Clarithromycin 500 mg Powder for Solution for Infusion is indicated whenever parenteral therapy is required for treatment of infections caused by susceptible organisms in the following conditions;

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

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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

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

4.3 Contraindications
- Clarithromycin is contraindicated in patients with known hypersensitivity to clarithromycin, to any other macrolide antibiotics or to any of the excipients.
- Clarithromycin is contraindicated in patients with serious hepatic failure.
• Clarithromycin and ergot derivatives should not be co-administered (see section 4.5).
• Concomitant administration of clarithromycin and any of the following active substances is contraindicated: cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels have been reported in patients receiving either of these active substances 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 (see section 4.5).
• Concomitant administration with simvastatin is contraindicated.
• Clarithromycin should not be administered to hypokalaemic patients (prolongation of QT-time, see section 4.4).

4.4 Special warnings and precautions for use
• Clarithromycin should be reserved for documented Group A beta-hemolytic streptococcal pharyngitis when treatment with beta-lactams cannot be used.
• Clarithromycin is mainly excreted by the liver. Therefore, clarithromycin should be administered with caution in patients with impaired hepatic function, especially in patients with impaired renal function.
• When renal function is poor, dosage of clarithromycin should be suitably reduced depending on the degree of the impairment (see section 4.2). In elderly patients, the possibility of renal impairment should be considered.
• Clarithromycin therapy for H. pylori may select for drug-resistant organisms.
• Patients who are hypersensitive to lincomycin or clindamycin may also be hypersensitive to clarithromycin. Therefore, caution is required when prescribing clarithromycin for such patients.
• 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.
• Attention should be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.
• Pseudomembranous colitis has been reported with the use of broad-spectrum antibiotics. Therefore, it is important to consider its diagnosis in patients who develop severe diarrhoea during or after therapy with clarithromycin.
• As known for other macrolides, clarithromycin may cause exacerbation or aggravation of myasthenia gravis and should therefore be used with caution in patients with myasthenia gravis.
• Due to a risk of prolonged QT-interval, clarithromycin should be used with caution in patients with a coronary vessel disease, a history of ventricular arrhythmia, severe cardiac insufficiency, non-compensated hypokalemia and/or hypomagnesemia, bradycardia (<50 bpm), or when co-administered with other medicinal products with a QT-prolonging effect. Clarithromycin should not be used in patients with congenital or documented acquired QT prolongation (see sections 4.3 & 4.5).
• The use of clarithromycin should be considered with particular caution whenever a patient is receiving treatment with another medicinal product known to be substrate of CYP3A4, especially when patient is treated with a CYP3A4 substrate having narrow therapeutic index (like carbamazepin) and/or is metabolised to a large extent by this enzyme clarithromycin should not be used unless clearly indicated (see section 4.5).
• Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these medicinal products (see section 4.5).
• 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

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Cisapride, pimozide, terfenadine and astemizole
Clarithromycin has been reported to elevate plasma levels of cisapride, pimozide, astemizole, and terfenadine. Increased levels of these drugs may result in increased risk of ventricular rhythm disorders, especially Torsades de Pointes.
Concomitant administration of clarithromycin and any of these medicinal products is contraindicated (see section 4.3).

Ergotamine/dihydroergotamine
Post-marketing reports indicate that co administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system.
Concomitant administration of clarithromycin and these medicinal products is contraindicated (see section 4.3).

The effect of other medicinal products on clarithromycin:
Clarithromycin is metabolised by the enzyme CYP3A4. Hence, strong inhibitors of this enzyme may inhibit the metabolism of clarithromycin, resulting in increased plasma concentrations of clarithromycin.
Concomitant administration of clarithromycin and antimycotics of the azole class (fluconazole, itraconazole, ketoconazole) increases the risk of cardial toxicity (prolonged QT-interval, Torsades des Pointes).

Fluconazole:
Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14(R)-hydroxy-clarithromycin were not significantly affected by concomitant administration of fluconazole.

Ritonavir:
Ritonavir (200 mg three times daily) have been shown to inhibit the metabolism of clarithromycin (500 mg twice daily), with an increase in Cmax, Cmin and AUC of 31, 182 and 77%, respectively, when co-administered with ritonavir. Formation of the active 14-OH-hydroxy metabolite was almost completely inhibited. A general dose reduction is probably not required in patients with normal renal function, but the daily dose of clarithromycin should not exceed 1g. Dose reduction should be considered in patients with renal impairment. For patients with a creatinine clearance of 30 to 60 ml/min (0.5 - 1 ml/s), the clarithromycin dose should be reduced with 50%, and at a creatinine clearance of < 30 ml/min (<0.5 ml/s) the dose should be reduced with 75%.

Medicinal Products that are inducers of CYP3A4 (e.g. efavirenz, nevirapine, rifampicin, phenytoin, carbamazepine, phenobarbital, St. Johns wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to a reduced efficacy.

Concomitant administration of rifabutin and clarithromycin resulted in an increase and decrease, respectively, in serum levels, followed by an increased risk of uveitis.

A 39% reduction in AUC for clarithromycin and a 34% increase in AUC for the active 14-OH-hydroxy metabolite have been seen when clarithromycin was used concomitantly with the CYP3A4 inducer efavirenz.

The effect of clarithromycin on other medicinal products
Clarithromycin is an inhibitor of the metabolizing enzyme CYP3A4 and the transport protein P-glycoprotein. The degree of inhibition with different CYP3A4 substrates is difficult to predict. Hence, clarithromycin should not be used during treatment with other medicinal
products that are substrates for CYP3A4, unless plasma levels, therapeutic effect or adverse events of the CYP3A4 substrate can be closely monitored. A dose reduction may be necessary.

Sildenafil, tadalafil, and vardenafil
Each of these phosphodiesterase inhibitors is metabolized, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co administration of clarithromycin with sildenafil, tadalafil or vardenafil may result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when co administered with clarithromycin.

Co-administration with medicinal products with a potential to prolong QT-interval: Cases of torsades de pointes has been reported in patients where clarithromycin has been co-administered with quinidine or disopyramide. These combinations should therefore be avoided, or plasma levels of quinidine or disopyramide closely monitored to allow dose adjustment.

HMG-CoA redactase inhibitors:
Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these medicinal products. Rhabdomyolysis in association with increased plasma concentrations have in rare cases been reported in patients treated with clarithromycin and simvastatin or lovastatin. Clarithromycin may produce a similar interaction with atorvastatin and a lesser interaction with cerivastatin. When treatment with clarithromycin is indicated in patients receiving statin treatment, therapy with statins should be suspended during the course of treatment.

Tolterodine
The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.

Benzodiazepines
When midazolam was co-administered with clarithromycin tablets (250mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A4, especially triazolam but also alprazolam. For benzodiazepines which are not metabolised by CYP3A4 (temazepam, nitrazepam, lorazepam) an interaction with clarithromycin is unlikely.

Omeprazole
The AUC of omeprazole is increased by 89% when administered concomitantly with clarithromycin for H. pylori eradication; however the change in the mean 24-hour gastric pH value from 5.2 (omeprazole alone) to 5.7 (omeprazole + clarithromycin) is not considered clinically significant.

There are no in-vivo human data available describing an interaction between clarithromycin and the following drugs: aprepitant, eletriptan, halofantrine, and ziprasidone. However, because in vitro data suggest these drugs are CYP3A substrates, caution should be used when they are co-administered with clarithromycin. Eletriptan should not be co-administered with CYP3A inhibitors such as clarithromycin. There have been spontaneous or published reports of drug interactions of CYP3A inhibitors, including clarithromycin, with cyclosporine, tacrolimus, methylprednisolone, vinblastine, and cilostazol.
Cyclosporin, tacrolimus and sirolimus:
Concomitant use of oral clarithromycin has resulted in more than a 2-fold increase of the C_{min} levels of both cyclosporin and tacrolimus. Similar effects are also expected for sirolimus. When initiating treatment with clarithromycin in patients already receiving any of these immunosuppressive agents, cyclosporin, tacrolimus or sirolimus plasma levels must be closely monitored and their doses decreased as necessary. When clarithromycin is discontinued in these patients, close monitoring of plasma levels of cyclosporine, tacrolimus or sirolimus, is again necessary to guide dose adjustment.

Digoxin and other active substances transported by P-glycoprotein
The concentration of the Pgp substrate digoxin may be increased when co-administered with clarithromycin. Monitoring of plasma levels of digoxin should be considered when co-treatment with clarithromycin is initiated or terminated since a dose adjustment may be warranted.

Anti-diabetic products
After concomitant administration of Clarithromycin with insulin and other anti-diabetic medicinal products hypoglycaemia has been observed. The mechanism for this phenomenon is not fully understood, though it may be related to pharmacokinetic interaction between clarithromycin and some oral antidiabetics. In healthy subjects, the use of clarithromycin 250 mg twice daily for two days increased glibenclamide plasma levels (0.875 mg single dose) with 1.3 fold, possibly by inhibiting P-glycoprotein in the intestinal wall. In a study in healthy volunteers, clarithromycin use (250 mg twice daily for 5 days) increases the plasma levels of repaglinide (0.25 mg single dose) with 40%, possibly by inhibiting CYP3A4 enzymes by clarithromycin.

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

Theophylline:
The administration of clarithromycin to patients who are receiving theophylline has been associated with an increase in serum theophylline levels and potential theophylline toxicity.

Zidovudine:
Simultaneous oral administration of clarithromycin and zidovudine to HIV infected adult patients may result in decreased steady-state zidovudine levels. This can be largely avoided by staggering the doses of clarithromycin and zidovudine by 1-2 hours. No such reaction has been reported in children.

Colchicine
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)

Phenytoin and valproate
There have been spontaneous or published reports of interactions with CYP3A inhibitors, including clarithromycin, and drugs not thought to be metabolised by CYP3A, including phenytoin and valproate. Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased concentrations have been reported.

Bidirectional pharmacokinetic interactions
Atazanavir
Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to
clarithromycin and a 70% decrease in exposure to \(14(\text{R})\)-hydroxylclarithromycin, with a 28% increase in the AUC of atazanavir.

Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function.

For patients with moderate renal function (creatinine clearance 30 to 60 ml/min), the dose of clarithromycin should be decreased by 50%.

For patients with creatinine clearance <30 ml/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation, such as immediate-release tablets, sachet, or paediatric suspensions (not all presentations may be marketed).

Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

**Itraconazole**

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction: Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin.

Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

**Saquinavir**

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bidirectional drug interaction.

Concomitant administration of clarithromycin (500 mg bid) and saquinavir (soft gelatine capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state area under the curve (AUC) and maximum concentration (Cmax) values of saquinavir, which were 177% and 187% higher than those seen with saquinavir alone.

Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin alone.

No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied.

Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule.

Observations from drug interaction studies done with unboosted saquinavir may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see section above, effect of other medicinal products on clarithromycin).

**4.6 Pregnancy and lactation**

**Pregnancy:**

Data on the use of clarithromycin during the first trimester of more than 200 pregnancies show no clear evidence of teratogenic effects or adverse effects on the health of the neonate. Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of abortions. To date no other relevant epidemiological data are available.

Data from animal studies have shown reproductive toxicity (see section 5.3). The risk for humans is unknown. Clarithromycin should only be used during pregnancy after a careful benefit/risk assessment.

**Lactation:**

Clarithromycin and its active metabolite are excreted in breast milk. Therefore, diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind. The benefit of treatment of the mother should be weighed against the potential risk for the infant.

**4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. When performing these activities the possible occurrence of the adverse reactions dizziness, vertigo, confusion and disorientation should be taken into account.
4.8 **Undesirable effects**

The most frequently reported events in adults taking clarithromycin were diarrhoea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%).

In this section undesirable effects are defined as follows:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

**Investigations:**

*Common:* Elevated blood urea nitrogen (BUN)

*Uncommon:* Prolongation of prothrombin time, elevated serum creatinine, altered liver function tests (increased transaminase levels).

*Very rare:* Hypoglycaemia has been observed especially after concomitant administration with antidiabetic medicinal products and insulin.

**Cardiac disorders:**

*Very rare:* QT prolongation, ventricular tachycardia and *torsade de pointes.*

**Blood and the lymphatic system disorders:**

*Uncommon:* Decreased leukocyte levels.

*Very rare:* Thrombocytopenia.

**Nervous system disorders:**

*Common:* Headache, smell alteration.

*Very rare:* Dizziness, vertigo, paraesthesia, convulsions.

**Ear and labyrinth disorders:**

*Rare:* Tinnitus.

*Very rare:* Reversible hearing loss.

**Gastrointestinal disorders:**

*Common:* Nausea, diarrhoea, vomiting, abdominal pain, dyspepsia, stomatitis, glossitis, reversible tooth and tongue discoloration, and taste perversion, i.e. metallic or bitter taste.

*Very rare:* Pancreatitis. Pseudomembranous colitis has been reported very rarely with clarithromycin, and may range in severity from mild to life threatening.

**Renal and urinary disorders:**

*Very rare:* Interstitial nephritis, renal failure.

**Skin and subcutaneous tissue disorders:**

*Very rare:* Stevens-Johnson syndrome and toxic epidermal necrolysis.

**Muscloskeletal and connective tissue disorders:**

*Uncommon:* Arthralgia, myalgia.

**Infections and infestations:**

*Common:* Oral monilia

As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms.

**Immune system disorders:**

*Uncommon:* Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis.
Hepato-biliary disorders:

*Uncommon*: Hepatic dysfunction, which is usually transient and reversible, hepatitis and cholestasis with or without jaundice.

*Very rare*: Fatal hepatic failure has been reported particularly in patients with pre-existing liver disease or taking other hepatotoxic medicinal products.

Psychiatric disorders:

*Uncommon*: Depression

*Very rare*: Anxiety, insomnia, hallucinations, psychosis, disorientation, depersonalisation, bad dreams and confusion.

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 4.4 and 4.5).

After taking this product, some cases of granulocytopenia have occurred; These symptoms disappear after stopping the treatment (see section 4.4).

4.9 Overdose

**Symptoms of intoxication:**
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. Symptoms of overdose may largely correspond to the profile of adverse reactions. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

**Therapy of intoxication:**
There is no specific antidote on overdose. Serum levels of clarithromycin cannot be reduced by haemodialysis or peritoneal dialysis.

Adverse reactions accompanying over dosage should be treated by gastric lavage and supportive measures. Severe acute allergic reactions may be seen very rarely, e.g. anaphylactic shock. At the first signs of hypersensitivity reactions therapy with clarithromycin must be discontinued and the required measures should be initiated immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

**General Properties**

**ATC classification**
Pharmacotherapeutic group: Macrolides
ATC Code: J01F A09

**Mode of Action**

Clarithromycin a semi-synthetic derivative of erythromycin, exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses 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-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal to or two-fold higher than the MICs of the parent compound except for *H. influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.
PK/PD Relationship

Clarithromycin is extensively distributed in body tissues and fluids. Because of high tissue penetration, intracellular concentrations are higher than serum concentrations.

The most important pharmacodynamic parameters for predicting macrolide activity are not conclusively established. The time above MIC (T/MIC) may correlate best with efficacy for clarithromycin, however since clarithromycin concentrations achieved in respiratory tissues and epithelial lining fluids exceed those in plasma, using parameters based on plasma concentrations may fail to predict accurately the response for respiratory tract infections.

Mechanism of resistance

Resistance mechanisms against macrolide antibiotics include alteration of the target site of the antibiotic, or are based on the modification and/or active efflux of the antibiotic.

Resistance development can be mediated via chromosomes or plasmids or be induced to exist constitutively. Macrolide-resistant bacteria generate enzymes which lead to methylation of residual adenine at ribosomal RNA and consequently to inhibition of the antibiotic binding to the ribosome. Macrolide-resistant organisms are generally cross-resistant to lincosamides and streptogramine B based on methylation of the ribosomal binding site.

Clarithromycin ranks among the strong inducers of this enzyme as well. Furthermore, macrolides have a bacteriostatic action by inhibiting the peptidyl transferase of ribosomes. A complete cross-resistance exists among clarithromycin, erythromycin and azithromycin. Methicillin-resistant staphylococci and penicillin-resistant Streptococcus pneumonia are resistant to macrolides such as clarithromycin.

Breakpoints

The following breakpoints for clarithromycin, separating susceptible organisms from resistant organisms, have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST) 2010-04-27 (v 1.1)

<table>
<thead>
<tr>
<th>Species-related breakpoints (S&lt;R&gt;)</th>
<th>Non-species related breakpoints(^A) S&lt;R&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clarithromycin(^B,C)</strong></td>
<td><strong>RD</strong> -- -- -- 1/2 -- 0.25/0.5 0.25/0.5 IE 1/32(^D) 0.25/0.5 -- -- -- -- IE</td>
</tr>
</tbody>
</table>

A. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes. However, pharmacodynamic data for calculation of macrolide, lincosamides and streptogramins non-species related breakpoints are not robust, hence IE.

B. Erythromycin can be used to determine the susceptibility of the listed bacteria to the other macrolides (azithromycin, clarithromycin and roxithromycin)

C. Clarithromycin is used for the eradication of H. pylori (MIC ≤0.25 mg/L for wild type isolates).
D. The correlation between H. influenzae macrolide MICs and clinical outcome is weak. Therefore, breakpoints for macrolides and related antibiotics were set to categorise wild type H. influenzae as intermediate.

Clarithromycin is used for the eradication of H. pylori; minimum inhibitory concentration (MIC) ≤ 0.25 μg/ml which has been established as the susceptible breakpoint by the Clinical and Laboratory Standards Institute (CLSI).

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

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

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic, Gram-positive microorganisms</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus group F</em></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium diphtheriae</em></td>
<td></td>
</tr>
<tr>
<td>Aerobic, Gram-negative microorganisms</td>
<td></td>
</tr>
<tr>
<td><em>Bordetella pertussis</em></td>
<td></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td></td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td></td>
</tr>
<tr>
<td><em>Legionella spp.</em></td>
<td></td>
</tr>
<tr>
<td>Anaerobic microorganisms</td>
<td></td>
</tr>
<tr>
<td><em>Clostridium spp., other than C. difficile</em></td>
<td></td>
</tr>
<tr>
<td>Other microorganisms</td>
<td></td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td></td>
</tr>
<tr>
<td><em>Chlamydophila pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Chlamyphilapitacci</em></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium spp.</em></td>
<td></td>
</tr>
<tr>
<td>Species for which acquired resistance may be a problem#</td>
<td></td>
</tr>
<tr>
<td>Aerobic, Gram-positive microorganisms</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus group A</em>, C, G</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus group B</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus viridans</em></td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus spp</em></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus, methicillin-susceptible and methicillin-resistant</em></td>
<td></td>
</tr>
</tbody>
</table>
**Streptococcus pneumoniae***

**Staphylococcus epidermidis**

**Aerobic, Gram-negative microorganisms**

**Haemophilus influenzae**

**Helicobacter pylori**

**Anaerobic microorganisms**

**Bacteroides spp.**

**Peptococcus/Peptostreptococcus spp.**

**Inherently resistant microorganisms**

**Aerobic, Gram-negative microorganisms**

**Pseudomonas aeruginosa**

**Acinetobacter**

**Enterobacteriaceae**

**Anaerobic microorganisms**

**Fusobacterium spp.**

**Other microorganisms**

**Mycobacterium tuberculosis**

# ≥ 10% resistance in at least one country of the European Union

* Species against efficacy has been demonstrated in clinical investigations (if susceptible)

+ Indicates species for which a high rate of resistance (i.e. greater than 50%) have been observed in one or more area/country/region(s) of the EU

§ Breakpoints for macrolides and related antibiotics were set to categorise wild type *H. influenzae* as intermediate

**Other information:**

Susceptibility and resistance of *Streptococcus pneumoniae* and *Streptococcus* spp. to clarithromycin can be predicted by testing erythromycin.

Most available clinical experience from controlled randomised clinical trials indicate that clarithromycin 500 mg twice daily in combination with another antibiotic e.g. amoxicillin or metronidazole and e.g. omeprazole (given at approved levels) for 7 days achieve > 80% *H. pylori* eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant *H. pylori* isolates. Hence, local information on the prevalence of resistance and local therapeutic guidelines should be taken into account in the choice of an appropriate combination regimen for *H. pylori* eradication therapy. Furthermore, in patients with persistent infection, potential development of secondary resistance (in patients with primary susceptible strains) to an antimicrobial agent should be taken into the considerations for a new retreatment regimen.

5.2 **Pharmacokinetic properties**

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

25
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 500 mg IV dose over 60 minutes, about 33% clarithromycin and 11% 14-hydroxylclarithromycin is excreted in the urine at 24 hours.

5.3 Preclinical safety data

In 4-week-studies in animals, toxicity of clarithromycin was found to be related to the dose and to the duration of the treatment. In all species, the first signs of toxicity were observed in the liver, in which lesions were seen within 14 days in dogs and monkeys. The levels of systemic exposure at which this toxicity occurred are not known in detail, but toxic doses (300 mg/kg/day) were clearly higher than the therapeutic doses recommended for humans. Other tissues affected included the stomach, thymus and other lymphoid tissues as well as the kidneys. At near therapeutic doses conjunctival injection and lacrimation occurred only in dogs. At a dose of 400mg/kg/day some dogs and monkeys developed corneal opacities and/or oedema.

In vitro and in vivo studies showed that clarithromycin did not have genotoxic potential.

Studies on reproduction toxicity showed that administration of clarithromycin at doses 2x the clinical dose in rabbit (iv) and 10x the clinical dose in monkey (po) resulted in an increased incidence of spontaneous abortions. These doses were related to maternal toxicity. No embryotoxicity or teratogenicity was generally noted in rat studies. However, cardiovascular malformations were observed in two studies in rats treated with doses of 150 mg/kg/d. In mice at doses 70x the clinical dose, cleft palate occurred at varying incidences (3-30%).

Clarithromycin has been found in the milk of lactating animals.

In 3-day old mice and rats, the LD$_{50}$ values were approximately half those in adult animals. Juvenile animals presented similar toxicity profiles to mature animals although enhanced nephrotoxicity in neonatal rats has been reported in some studies. Slight reductions in erythrocytes, platelets and leukocytes have also been found in juvenile animals.

Clarithromycin has not been tested for carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactobionic acid
Sodium Hydroxide

6.2 Incompatibilities

None known. However, clarithromycin should only be diluted with the diluents recommended in section 6.6.

6.3 Shelf life

As packaged for sale: 2 years.

In use:

After reconstitution with 10 ml of Water for Injections, chemical and physical in-use stability has been demonstrated for 24 hours at 5°C - 25°C.

After dilution in 250 ml of a recommended diluent (see section 6.6), chemical and physical stability has been demonstrated for 6 hours at 25°C or 24 hours at 5°C.

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

After reconstitution/dilution: see section 6.3.

6.5 Nature and contents of container
20 ml Type I flint tubular glass vial with a rubber plug and flip off seal.

Vials are packed in units of 1, 4 and 6.

6.6 Special precautions for disposal and other handling
Clarithromycin should be administered into one of the larger proximal veins as an IV infusion over 60 minutes, using a solution concentration of about 2 mg/ml. Clarithromycin should not be given as a bolus or an intramuscular injection.

Reconstitution of powder (Step 1)
Add 10 ml of sterile Water for Injections into the vial and shake.

Dilution (Step 2)
Add 10 ml of the reconstituted solution from Step 1 to 250 ml of a suitable diluent to provide a 2 mg/ml solution.

Recommended diluents
5% dextrose in Lactated Ringer's Solution
5% dextrose
Lactated Ringer's solution
5% dextrose in 0.3% sodium chloride
5% dextrose in 0.45% sodium chloride
0.9% sodium chloride

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

7 MARKETING AUTHORISATION HOLDER
Hospira UK Limited
Queensway, Royal Leamington Spa,
Warwickshire, CV31 3RW

8 MARKETING AUTHORISATION NUMBER(S)
PL 04515/0163

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/11/2011

10 DATE OF REVISION OF THE TEXT
30/11/2011
PRODUCT INFORMATION LEAFLET

Hospira

PACKAGE LEAFLET: INFORMATION FOR THE USER

Clarithromycin 500 mg Powder for Infusion

Read all of this leaflet carefully before you start using this medicine.
Keep this leaflet. You may need to read it again.
If you have any further questions, ask your doctor or pharmacist.
If any of the side effects gets serious, or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Clarithromycin Powder for Infusion is and what it is used for
2. Before you use Clarithromycin Powder for Infusion
3. How to use Clarithromycin Powder for Infusion
4. Possible side effects
5. How to store Clarithromycin Powder for Infusion
6. Further information

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

Clarithromycin Powder for Infusion is an antibiotic medicine. The medicine is presented in the form of a powder for solution for infusion i.e. a powder, which is made into a solution, which can be given as a slow injection via a drip.

Clarithromycin Powder for Infusion is a type of antibiotic cated macrolides. Antibiotics stop the growth of bacteria (bugs) which cause infections. It is used when an intravenous (injection into a vein) antibiotic is required to treat severe infections.

It is used to treat infections such as:
- Chest infections e.g. bronchitis, pneumonia
- Throat and sinus infections
- Skin and tissue infections

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

Do not take Clarithromycin if you are taking any one of the following medicines:
- terfenadine or astemizole (for hay fever or allergy),
- cisapride (for stomach disorders),
- pimozide (for certain severe mental disorders),
- ergotamine or dihydroergotamine (for hypotension and migraine),
- colchicine (usually taken for gout),

Combining Clarithromycin with these drugs may cause serious disturbances in heartbeat rhythm or serious side effects.

If taken with Clarithromycin, the levels and therefore the effects of the following listed medicines may be increased:
- Digoxin, quinidine or disopyramide (heart drugs)
- Warfarin (blood thinner )
- Ergotamine or dihydroergotamine (used for migraine)
- Carbamazepine, valproate or phenytoin (drugs for epilepsy)
- Colchicine (for gout)
- Theophylline (helps breathing)
- Terfenadine or astemizole (for hay fever or allergy)
- Triazolam, alprazolam or midazolam (sedatives)
- Lovastatin or simvastatin (drugs for high cholesterol)
- Cisapride or omeprazole (for stomach disorders) and
- Pimozide (an antipsychotic drug)

Clarithromycin may interact with the antiviral (HIV) drugs in the following manner:
- Clarithromycin may lower the levels of zidovudine.
2. BEFORE YOU USE CLARITHROMYCIN POWDER FOR INFUSION

Do not use Clarithromycin Powder for Infusion if you;
- know that you are allergic (hypersensitive) to clarithromycin or other macrolide antibiotics (such as erythromycin or azithromycin) or any of the other ingredients in the product.
- are taking medicines called ergotamine or dihydroergotamine tablets, or use ergotamine inhalers for migraine. Consult your doctor for advice on alternative medicines.
- are taking medicines called terfenadine and astemizole (widely taken for hay fever and allergies) or ciprofloxacin (for stomach disorders) or pimozide (for mental problems) as combining these drugs can sometimes cause serious disturbances in heart rhythm. Consult your doctor for advice on alternative medicines.
- are taking simvastatin (to reduce cholesterol levels)
- know that your blood potassium is abnormally low
- you have severe liver problems

Take special care with Clarithromycin Powder for Infusion if:
- you have liver or kidney problems
- you have H. pylori Infection
- you or someone in your family has had an allergic reaction to certain other antibiotics (Incomycin and clindamycin). There is a risk of an allergic reaction to Clarithromycin as well (cross-hypersensitivity).
- you have heart problems (such as coronary vessel disease, slow or irregular heart beat or a weak heart) or if medicinal products are used at the same time which may affect the heart beat.
- you have low blood values or potassium and/or magnesium. The rhythm of heartbeat may become affected in such cases.
- you have myasthenia gravis (a disease affecting muscle functions) symptoms may become more severe if clarithromycin is used.
- you are taking colchicine (medicine used for the treatment of gout)

If you have any of the following conditions above speak to your doctor before using Clarithromycin.
- Ritonavir may increase the levels of Clarithromycin.
- Atazanavir and Saquinavir: taking these drugs with Clarithromycin may increase both the levels of Atazanavir (or Saquinavir) and Clarithromycin.
- Nevirapine and Efavirenz may lower the levels of Clarithromycin.

Other Interactions Include:
- Rifabutin (an antibiotic effective against some infections) may lower the levels of Clarithromycin.
- Itraconazole (an anti-fungal drug) taken together with Clarithromycin may increase the levels of both medicines.
- Fluconazole, another anti-fungal drug, may increase the level of Clarithromycin.
- Sildenafil, tadalafil or vardenafil (for treating erectile dysfunction). Taking these drugs with Clarithromycin may increase both their levels.
- Tolterodine (to treat symptoms of overactive bladder syndrome). In certain patients, the levels of tolterodine may be increased when taken with Clarithromycin.
- Methylprednisolone (a corticosteroid to treat inflammation).
- Vinblastine (a chemotherapy agent used to treat cancer).
- Ziprasidone (antipsychotic drugs).
- Elnpriptan (used for migraine).
- Halofantrine (used to treat malaria).
- Aproton (used to prevent vomiting during chemotherapy).
- Cisplatin (used to improve circulation in the legs).
- Rifampicin (to treat tuberculosis).
- Any beta-lactam antibiotics and
- Tacrolimus or cyclosporin (for organ transplants).
- St. John’s Wort (herbal product to treat depression).
- Phencobarbital (drug for epilepsy).

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Experience of treating pregnant women and nursing mothers is limited. Pregnant women and nursing mothers should be treated only if the expected benefits outweighs the possible risks.

Driving and using machines
Do not drive or use machines, if you suffer from one of the following side effects: dizziness, confusion or disorientation.
3. HOW TO USE CLARITHROMYCIN POWDER FOR INFUSION

Clarithromycin Powder for Infusion is prepared by dissolving the powder in the vial in sterile water. The solution is then added to a larger volume of a solution such as sodium chloride 0.9% before it is given to you. It will be given to you by a slow injection via a drip into a vein over 60 minutes.

This medicine will usually be given for two to five days, and should be changed to oral clarithromycin treatment (tablets) when appropriate.

Treatment for Adults and the Elderly:
The usual dose is 1.0 gram daily split into two 500 mg doses.

Children under 12 years old:
This medicine is not recommended for children.

Patients with kidney problems:
Your doctor will be especially careful when giving you this medicine if your kidneys are not working properly, and the dose will be reduced.

If you are concerned about how much medicine you have been given or how often you have been given it, please tell your doctor or nurse.

4. POSSIBLE SIDE EFFECTS

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

If any of the following happen, tell the doctor immediately:
- Allergic reactions ranging from mild itchy skin eruption to shock (drop of blood pressure, restlessness, weak rapid pulse, clammy skin, reduced consciousness). These allergic reactions may occur uncommonly.

Very rare side effects (seen in less than 1 person in 10,000) include:
- Difficulty sleeping, bad dreams, hallucinations, disorientation
- Confusion, depersonalisation, change in the sense of reality and feeling panicky
- Dizziness, vertigo, numbness or pins and needles, fits (convulsions)
- Changes in heart beat/rhythm
- Hearing loss (usually reversible on withdrawal of treatment)
- Low blood sugar levels or a “hypo” in diabetic patients
- Kidney problems
- Liver problems
- Nausea, vomiting, abdominal pain and back pain (pancreatitis)
- Reduction in blood cells (thrombocytopenia) with bruises and tendency to bleed
- Severe condition with (high) fever, red spots on the skin, joint pains and/or eye infection (Stevens-Johnson syndrome)

Clarithromycin may worsen the symptoms of myasthenia gravis (a condition in which the muscles become weak and tire easily) in patients who already suffer from this condition.

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

5. HOW TO STORE CLARITHROMYCIN POWDER FOR INFUSION

For single use. Discard any unused contents.
Keep the vial in the outer container in order to protect from light.
Keep out of the reach and sight of children.

Do not use Clarithromycin Powder for Infusion after the expiry date which is stated on the label and carton. The expiry date refers to the last day of the month.
• severe prolonged diarrhoea. This may indicate a very rare inflammation of the large intestine (pseudomembranous colitis).
• a severe hypersensitivity reaction involving mucous membranes, with (high) fever, red spotted skin, joint pain and or inflammation of the eyes (Steven-Johnson syndrome) or if you experience a severe sudden hypersensitivity reaction with fever and skin blisters/skin disintegration (toxic epidermal necrolysis). These serious side effects may occur very rarely.

Other possible side effects include:

Common side effects (seen in more than 1 in 100 patients, but less than 1 in 10) include:
• Redness, tenderness or pain around the injection site
• Stomach problems such as nausea, vomiting, indigestion, stomach pains or diarrhoea.
• Change in sense of smell and taste
• Inflammation of the mouth or tongue, tongue discoloration, thrush in the mouth (causing soreness of the mouth sometimes accompanied by white spots)
• Teeth discoloration (this can usually be corrected by professional cleaning)
• Headache
• Changes in blood test levels

Uncommon side effects (seen in more than 1 in 1,000 patients, but less than 1 in 100) include:
• Depression
• Joint and muscle pain
• Decrease in the number of a type of blood cell (leucocytes), which makes infections more likely
• Allergic reactions which may range from skin rash, swollen itchy skin and skin rashes to difficulty in breathing and dizziness
• Liver or gall bladder problems, yellowing of the skin or eyes (jaundice)

Rare side effects (seen in more than 1 in 10,000 patients but less than 1 in 1,000) include:
• Ringing in the ears (tinnitus)

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Clarithromycin Powder for Infusion contains
• The active substance is clarithromycin
• The other ingredient is lactobionic acid

What Clarithromycin Powder for Infusion looks like and contents of the pack
Clarithromycin Powder for Infusion is an antibiotic medicine. The medicine is presented in the form of a powder for solution for infusion i.e. a powder which is made into a solution which can be given as a slow injection via a drip.

Each vial of Clarithromycin Powder for Infusion contains 500 mg of clarithromycin. It is available in packs of 1, 4 and 6 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder
Hospira UK Limited,
Queensway,
Royal Leamington Spa
Warwickshire,
CV31 3RW

Manufacturer
Strides Arcolab
Polska Sp z o o,
Poland

This leaflet was last approved in January 2011
UKPAR Clarithromycin 500 mg Powder for Solution for Infusion  PL 04515/0163

LABELLING

Carton – 1 vial

Clarithromycin 500 mg Powder for Infusion:
Each vial contains:
Clarithromycin 500 mg and Lactobionic acid.

PL 04515/0163
For single use
Discard any unused contents
To be used as directed by a medical practitioner
Keep vial in the outer carton
KEEP OUT OF REACH AND SIGHT OF CHILDREN

Barcode @ 80%

Batch No.:
Exp.

Vial label

Clarithromycin 500 mg Powder for Infusion
For IntraVenous Use
1 Vial

PL 04515/0163

Dosage and Administration: Please read enclosed leaflet
Powder for Infusion: Each vial contains
Clarithromycin 500 mg and Lactobionic acid.
For single use: Discard any unused contents
To be used as directed by a medical practitioner
Keep vial in the outer carton
KEEP OUT OF REACH AND SIGHT OF CHILDREN

Code No. RK/00038/1303/300/95
MA Holder:
Hospira UK Limited
Queensway, Royal Leamington Spa,
Warwickshire CV31 3RJ
UKPAR Clarithromycin 500 mg Powder for Solution for Infusion PL 04515/0163

Carton – 4 vials
UKPAR Clarithromycin 500 mg Powder for Solution for Infusion  PL 04515/0163

Carton – 6 vials