

Clarithromycin 250 mg Film Coated Tablets

Clarithromycin 500 mg Film Coated Tablets

PL 20897/0001

PL 20897/0002

UKPAR

TABLE OF CONTENTS

Lay summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 14
Summary of product characteristics	Page 15
Product information leaflet	Page 35
Labelling	Page 39

Clarithromycin 250 mg Film Coated Tablets

Clarithromycin 500 mg Film Coated Tablets

PL 20897/0001-2

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Clarithromycin 250 mg Film Coated Tablets and Clarithromycin 500 mg Film Coated Tablets (Product Licence numbers: 20897/0001-2).

Clarithromycin is an antibiotic belonging to a group of medicines known as the macrolides. Antibiotics stop the growth of bacteria that cause infections. Clarithromycin Film Coated Tablets are used to treat respiratory infections such as bronchitis and pneumonia, throat and sinus infections, skin and soft tissue infections, and infections in patients with duodenal ulcers.

The data submitted in support of these applications for Clarithromycin 250 mg Film Coated Tablets and Clarithromycin 500 mg Film Coated Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

Clarithromycin 250 mg Film Coated Tablets

Clarithromycin 500 mg Film Coated Tablets

PL 20897/0001-2

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 7
Clinical assessment (including statistical assessment)	Page 8
Overall conclusions and risk benefit assessment	Page 13

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Clarithromycin 250 mg Film Coated Tablets and Clarithromycin 500 mg Film Coated Tablets (PL 20897/0001-2) to Helm AG on 11 July 2008. These tablets are only available by prescription.

These applications are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC. The applicant claims that the proposed products are generic versions of the original product Klaricid[®] tablets. These original products were licensed to Abbott Laboratories UK Limited in the UK on 9 April 1991 (Klaricid[®] tablets 250 mg, PL 00037/0211) and 24 March 1994 (Klaricid[®] tablets 500 mg, PL 00037/0254) so the 10-year period of data exclusivity has expired.

Clarithromycin tablets are indicated for the treatment of infections caused by susceptible organisms. Indications include lower respiratory tract infections, such as pneumonia and acute and chronic bronchitis, and upper respiratory tract infections, such as sinusitis and pharyngitis. Clarithromycin tablets are also indicated in skin and soft tissue infections of mild to moderate severity. Clarithromycin tablets in the presence of acid suppression effected by omeprazole or lansoprazole are also indicated for the eradication of *H. pylori* in patients with duodenal ulcers.

PHARMACEUTICAL ASSESSMENT

DRUG INGREDIENT

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.

Active clarithromycin is 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 the current storage instructions.

DRUG PRODUCT

Description and Composition of the Drug Product

The tablets are yellow-coloured, elliptical, biconvex, film-coated tablets with smooth surfaces. As well as the active ingredient, these film coated tablets contain croscarmellose sodium, pregelatinised starch, silicon dioxide, povidone, stearic acid, magnesium stearate, talc, microcrystalline cellulose, propylene glycol and opadry OY-S32924. All excipients are well-known, of pharmacopoeia grade and widely used in solid dose oral products. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of opadry OY-S32924, which complies with an in-house specification (in the absence of a Ph Eur monograph, this is acceptable). Satisfactory certificates of analysis have been provided for all excipients.

BSE statements are provided by all suppliers. All inactive ingredients are of synthetic, mineral or vegetable origin except stearic acid. The supplier of the stearic acid states that it is abstracted from cattle tallow of continental source and is sufficiently severely treated to prevent TSE transmission.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

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 has been carried out on batches of each strength. The results are satisfactory.

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 tablets are packed in blister packs with an outer pack and package leaflet. Pack sizes for both tablet strengths are 10, 12, 14, 20, 30, 50, 500 tablets, although not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all primary packaging have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. This medicinal product does not require any special storage conditions.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

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

PRECLINICAL ASSESSMENT

These applications are for products that are generic versions of Klaricid[®] tablets (Abbott Laboratories UK Limited), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

Background

Of the Active Ingredient: Clarithromycin, a semi synthetic derivative of erythromycin [6-O-methyl erythromycin-A] is a macrolide antibiotic that is active against aerobic and anaerobic bacteria, both gram positive and gram negative. Its primary efficacy is against pathogens causing both upper and lower respiratory tract infections and soft tissue infections and *H.pylori*.

Of the Application: The basis of these applications is that the proposed products are generic to Klaricid (Abbott Laboratories Ltd) which has been in clinical use since 1990, and since 1991 in the UK. The relevant article is 10.1, based on directive 83/2001/EC, and two bioequivalence studies have been submitted. The MAA form cites Klacid 500mg from Abbott (UK) as the innovator product and the products used for bioequivalence are Klacid (Abbott, Germany) for the 250mg bioequivalence study and Klacid 500mg tablets (Abbott S.p.a, Italy) for the 500mg bioequivalence study.

Indications

The indications sought are:

“Clarithromycin Tablets are indicated for treatment of infections caused by susceptible organisms. Indications include:

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

Upper respiratory tract infections for example, sinusitis and pharyngitis.

Clarithromycin Tablets are appropriate for initial therapy in community acquired respiratory infections and have been shown to be active in vitro against common and atypical respiratory pathogens as listed in section 5.1. “Pharmacodynamic properties”.

Clarithromycin Tablets are also indicated in skin and soft tissue infections of mild to moderate severity.

Clarithromycin Tablets in the presence of acid suppression effected by omeprazole or lansoprazole are also indicated for the eradication of *H. pylori* in patients with duodenal ulcers.

See Dosage and Administration section.

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

Assessor’s Comment:

The indications sought are identical to those of the brand leader Klaricid (UK) and are satisfactory.

Dose and Dose Regimen

The applicant proposes the following dosing schedule:

“Patients with respiratory tract/skin and soft tissue infections

Adults: The usual dose is 250 mg twice daily for 7 days although this may be increased to 500 mg twice daily for up to 14 days in severe infections.

Children older than 12 years: As for adults.

Children younger than 12 years: Use an appropriate clarithromycin paediatric preparation.

Eradication of *H. pylori* in patients with duodenal ulcers (Adults)

Triple Therapy (7 - 14 days)

Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with amoxicillin 1000 mg twice daily for 7 - 14 days.

Triple Therapy (7 days)

Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with metronidazole 400 mg twice daily for 7 days.

Triple Therapy (7 days)

Clarithromycin 500 mg twice daily and omeprazole 40 mg daily should be given with amoxicillin 1000 mg twice daily or metronidazole 400 mg twice daily for 7 days.

Triple Therapy (10 days)

Clarithromycin 500 mg twice daily should be given with amoxicillin 1000 mg twice daily and omeprazole 20 mg daily for 10 days.

Dual Therapy (14 days)

The usual dose of clarithromycin is 500 mg three times daily for 14 days. Clarithromycin should be administered with oral omeprazole 40 mg once daily for 14 days.

Elderly: As for adults.

Renal impairment: Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance < 30 ml/min). If adjustment is necessary, the total daily dosage should be reduced by half, e.g. 250 mg once daily or 250 mg twice daily in more severe infections.

Clarithromycin Tablets may be given without regard to meals as food does not affect the extent of bioavailability.”

Assessor’s Comment:

This Dose and Dose Regimen is in line with that of the brand leader Klaricid (UK) and is satisfactory.

Consideration for Paediatric use

There is no paediatric development programme for this product and there are no reasons to limit use of clarithromycin in children. The current formulation is not intended for use in children younger than 12 years. The reference product is authorised for use in children older than 12 years as a tablet and separate paediatric formulations are available for younger children. This application does not however concern paediatric formulations and an appropriate warning and advice that clarithromycin may be administered to children in paediatric formulations is included.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Summary

The pharmacokinetics of clarithromycin have been well established. The applicant has not submitted any new kinetic data but has submitted the required bioequivalence studies. This approach is acceptable. The metabolism / kinetics are non-linear and saturable at high doses of clarithromycin, but linear at the doses proposed.

Pharmacodynamics

Summary

The pharmacodynamics of clarithromycin has been well established. It is a semisynthetic derivative of erythromycin-A and is active against a wide variety of aerobic and anaerobic gram-positive or gram-negative bacterial strains. It binds to the 50S ribosomal unit inhibiting protein synthesis. The metabolite 14-hydroxy clarithromycin, is also active and synergistic with the parent compound.

Bioavailability and Bioequivalence

Bioavailability

The bioavailability of the generic compound was not assessed separately but as a part of the bioequivalence study that is addressed below.

Bioequivalence study

In accordance with requirements, the applicant has submitted two bioequivalence studies (250 and 500 mg) comparing the proposed tablets with the reference product. For a product with non-linear kinetics, a bioequivalence study is expected at each dose level proposed; hence the two studies. It should be noted that the studies used different reference products; one from Germany (Klacid 250mg) and once from Italy (Klacid 500mg), albeit both are from Abbott Laboratories. A summary of each study is provided below.

It is stated that the studies were performed in accordance with GCP/GLP guidelines. The studies were audited/monitored by a Clinical Research Organisation.

Clarithromycin in the plasma was assayed using LC/MS methodology. For details of the methodology and acceptability, including limits of quantification, the reader is referred to the pharmaceutical assessment.

Both were single-dose, block randomised, two-way crossover, two-period, controlled studies with an adequate sampling period pre-dose to 48 hours. Both clarithromycin and the active metabolite 14-OH-clarithromycin have been analysed in line with the guidelines.

BE Study:

250 mg tablets (*n*=24 subjects, male and female)

Analyte- Clarithromycin

Parameter	Test Product 250 mg	Reference Product 250 mg	Pt Est & CI 90%
AUC _{0-t} (ng*hr/ml)	4825.3 ± 1923.1	4842.40 ± 1361.0	
AUC _{0-inf} (ng*hr/ml)	5384.2 ± 2178.3	5399.0 ± 1475.0	1.065 (0.882 to 1.21)
C _{max} (ng/ml)	908.48 ± 423.7	877.76 ± 283.94	1.078 (0.86 to 1.24)
T _{1/2} (hrs)	3.46	3.9	

Analyte: 14 hydroxy-clarithromycin

Parameter	Test Product 250 mg	Reference Product 250 mg	Pt Est & CI 90%
AUC _{0-t} (ng*hr/ml)	5331.5 ± 1858.7	5057.1 ± 1477.5	
AUC _{0-inf} (ng*hr/ml)	5852.6 ± 1918.0	5584.2 ± 1588.8	1.055 (0.909 to 1.20)
C _{max} (ng/ml)	586.25 ± 226.9	571.25 ± 191.49	1.03 (0.86 to 1.21)
T _{1/2} : (hrs)	7.363	7.196	

500mg tablets (n=24 subjects, male and female)

Analyte- Clarithromycin

Parameter	Test Product 500 mg	Reference Product 500 mg	Pt Est & CI 90%
AUC _{0-t} (ng*hr/ml)	15698.0 ± 5857.5	15485.0 ± 8014.3	
AUC _{0-inf} (ng*hr/ml)	17135.0 ± 6025.4	16918.0 ± 8288.7	0.974 (0.829 to 1.23)
C _{max} (ng/ml)	2019.9 ± 822.5	1982.3 ± 1027.2	0.988 (0.83 to 1.249)
T _{1/2} : (hrs)	6.32	6.07	

Analyte: 14 hydroxy-clarithromycin

Parameter	Test Product 500 mg	Reference Product 500 mg	Pt Est & CI 90%
AUC _{0-t} (ng*hr/ml)	8317.6 ± 4526.6	8273.2 ± 3876.2	
AUC _{0-inf} (ng*hr/ml)	8722.4 ± 4620.1	8703.2 ± 3905.8	1.028 (0.807 to 1.244)
C _{max} (ng/ml)	737.57 ± 282.12	712.3 ± 326.04	1.018 (0.859 to 1.247)
T _{1/2} : (hrs)	7.61	7.79	

Assessor's Comments:

- The studies conform to the requirements of the CHMP guideline on Bioequivalence (CPMP/EWP/QWP/1401/98).
- The sampling time of 48 hours is considered adequate and the LC/MS methodology appears satisfactory. Furthermore, the residual area [(AUC_{inf} - AUC_t)/AUC_{inf}] is <20 % in both studies, confirming appropriate point of extrapolation.
- Moreover, the 14-OH-clarithromycin plasma concentrations are within range of previously reported values (C_{max} ~65% for 250mg study and 35% for the 500mg study).
- Comparative dissolution profiles of the reference products employed with the reference product in the UK are provided for both 250 and 500mg tablet strengths.

CLINICAL EFFICACY

Summary:

The dossier includes published clinical studies and it is accepted that efficacy of clarithromycin is established. There are no new efficacy data and none are required for an application based on Article 10.1. This is satisfactory.

CLINICAL SAFETY

Summary

The safety of clarithromycin has been established over the last 10 years. The QT prolongation and interaction with other medicines that affect QT interval have been emphasised in the SPC. There are few safety concerns arising out of the bioavailability / bioequivalence studies organised, conducted or sponsored by the applicant. The risk-benefit ratio is therefore considered favourable.

EXPERT REPORTS

A satisfactory expert report is provided by an appropriately qualified physician.

PRODUCT LITERATURE

The product literature (Summary of Product Characteristics, Patient Information Leaflet and product labelling) are satisfactory.

CONCLUSIONS

The pharmacological aspects of clarithromycin and the basis for the application are acceptable.

The applicant has fulfilled the requirement as per NfG on bioequivalence (CPMP/EWP/QWP/1401/98) in appropriately conducted studies. The efficacy and safety of the active are well known. It is accepted that the risk-benefit ratio is favourable for clarithromycin tablets.

Marketing authorisations can, therefore, be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Clarithromycin 250 mg Film Coated Tablets and Clarithromycin 500 mg Film Coated Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

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

EFFICACY

The efficacy of clarithromycin is well established.

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

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with Clarithromycin 250 mg Film Coated Tablets and Clarithromycin 500 mg Film Coated Tablets. The risk benefit is therefore considered to be positive.

Clarithromycin 250 mg Film Coated Tablets

Clarithromycin 500 mg Film Coated Tablets

PL 20897/0001-2

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the Marketing Authorisation application on 2 April 2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 13 May 2004
3	Following assessment of the application the MHRA requested further information relating to the clinical dossier on 5 November 2004 and the quality dossier on 31 December 2004. The applicant responded to the MHRA's requests, providing further information on the clinical dossier on 1 March 2005 and the quality dossier on 20 June 2005
4	Following assessment of the application the MHRA requested further information relating to the quality dossier on 22 July 2005 and the clinical dossier on 9 December 2005. The applicant responded to the MHRA's requests, providing further information on the quality dossier on 12 September 2005
5	Following assessment of the response the MHRA requested further information relating to the quality dossier on 16 September 2005. The applicant responded to the MHRA's requests, providing further information on the quality dossier on 27 June 2006
6	Following assessment of the response the MHRA requested further information relating to the quality dossier on 5 September 2006. The applicant responded to the MHRA's requests, providing further information on the quality dossier on 7 5 March 2007
7	The application was determined on 11 July 2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 250 mg Film Coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clarithromycin 250 mg Film Coated Tablets: Clarithromycin 250 mg/tablet

For excipients see section 6.1.

3 PHARMACEUTICAL FORM

Clarithromycin 250 mg Film Coated Tablets:

A yellow coloured, elliptical, biconvex film-coated tablet with smooth surface containing 250 mg of clarithromycin.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarithromycin Tablets are indicated for treatment of infections caused by susceptible organisms. Indications include:

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

Upper respiratory tract infections for example, sinusitis and pharyngitis.

Clarithromycin Tablets are appropriate for initial therapy in community acquired respiratory infections and have been shown to be active in vitro against common and atypical respiratory pathogens as listed in section 5.1. "Pharmacodynamic properties".

Clarithromycin Tablets are also indicated in skin and soft tissue infections of mild to moderate severity.

Clarithromycin Tablets in the presence of acid suppression effected by omeprazole or lansoprazole are also indicated for the eradication of *H. pylori* in patients with duodenal ulcers.

See Dosage and Administration section.

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

4.2 Posology and method of administration

Patients with respiratory tract/skin and soft tissue infections

Adults: The usual dose is 250 mg twice daily for 7 days although this may be increased to 500 mg twice daily for up to 14 days in severe infections.

Children older than 12 years: As for adults.

Children younger than 12 years: Use an appropriate clarithromycin paediatric preparation.

Eradication of *H. pylori* in patients with duodenal ulcers (Adults)

Triple Therapy (7 - 14 days)

Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with amoxicillin 1000 mg twice daily for 7 - 14 days.

Triple Therapy (7 days)

Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with metronidazole 400 mg twice daily for 7 days.

Triple Therapy (7 days)

Clarithromycin 500 mg twice daily and omeprazole 40 mg daily should be given with amoxicillin 1000 mg twice daily or metronidazole 400 mg twice daily for 7 days.

Triple Therapy (10 days)

Clarithromycin 500 mg twice daily should be given with amoxicillin 1000 mg twice daily and omeprazole 20 mg daily for 10 days.

Dual Therapy (14 days)

The usual dose of clarithromycin is 500 mg three times daily for 14 days.

Clarithromycin should be administered with oral omeprazole 40 mg once daily for 14 days.

Elderly: As for adults.

Renal impairment: Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance < 30 ml/min). If adjustment is necessary, the total daily dosage should be reduced by half, e.g. 250 mg once daily or 250 mg twice daily in more severe infections.

Clarithromycin Tablets may be given without regard to meals as food does not affect the extent of bioavailability.

4.3 Contraindications

Clarithromycin is contra-indicated in patients with known hypersensitivity to clarithromycin, other macrolide antibiotics or to any of the excipients in the tablet.

Clarithromycin and ergot derivatives must not be co-administered.

Concomitant administration of clarithromycin and any of the following drugs is contra-indicated: cisapride, pimozone and terfenadine. Elevated cisapride, pimozone 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.

Clarithromycin is contra-indicated in patients with hypokaliemia. This may result in QT prolongation.

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 or 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.

H. pylori organisms may develop resistance to clarithromycin.

4.5 Interaction with other medicinal products and other forms of interaction

As with other macrolide antibiotics the use of clarithromycin in patients concurrently taking drugs metabolised by the cytochrome P 450 system (eg. warfarin, ergot alkaloids, triazolam, midazolam, disopyramide, lovastatin, rifabutin, phenytoin, valproate, cyclosporin, tacrolimus, rifampicin, cisapride, methyl prednisolone, vinblastine, sildenafil, hexobarbital, alfentanil, pimozide, terfenadine, alprazolam, cilostazol and chinidin) may be associated with elevations in serum levels of these other drugs.

HMG-CoA reductase inhibitors:

Rhabdomyolysis, co-incident with the co-administration of clarithromycin, and HMG-CoA reductase inhibitors, such as lovastatin and simvastatin has been reported.

Further interactions:

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

As mentioned above 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.

The effects of digoxin may be potentiated with concomitant administration of Clarithromycin Tablets. 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 adult patients may result in decreased steady-state zidovudine levels. This can be largely avoided by staggering the doses of Clarithromycin Tablets and zidovudine by 1 - 2 hours. No such 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 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with $CL_{CR} < 30$ ml/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1g/day should not be co-administered with ritonavir.

Although the plasma concentrations of clarithromycin and omeprazole may be increased when they are administered concurrently, no adjustment to the dosage is necessary. At the dosages recommended, there is no clinically significant interaction between clarithromycin and lansoprazole. Increased plasma concentrations of clarithromycin may also occur when it is co-administered with aluminium oxide/magnesium hydroxide-antacids or ranitidine. No adjustment to the dosage is necessary.

Macrolides have been reported to have an effect on the metabolism of terfenadine/astemizole, in which case the terfenadine/astemizole values are elevated, which has, in individual cases, been shown to cause cardiac arrhythmias. Similar effects have also been reported with combined use of astemizole and other macrolides.

A concomitant administration of macrolide antibiotics with cyclosporine and bromocriptine may result in an increase of plasma levels of cyclosporine and bromocriptine. Consequently the dose of cyclosporine and bromocriptine needs to be decreased.

A potential cross-resistance of bacterial strains against clarithromycin and other macrolide antibiotics such as erythromycin and clindamycin needs to be considered. The concomitant administration of products belonging to this compound class is therefore not recommended.

There have been postmarketed reports of Torsade de Points 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

4.6 Pregnancy and lactation

The safety of clarithromycin during pregnancy and breast feeding of infants has not been established. Clarithromycin Tablets 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

Although clarithromycin is not expected to affect driving ability directly, side effects such as dizziness and vertigo may interfere with driving.

4.8 Undesirable effects

Infections and infestations:

Oral monilla, genital candidiasis

Blood and lymphatic system disorders:

Isolated cases of leukopenia and thrombocytopenia have been reported.

Immune system disorders:

Allergic reactions ranging from urticaria, mild skin eruptions and angioedema to anaphylaxis and rarely Stevens-Johnson syndrome / toxic epidermal necrolysis.

Metabolic disorders:

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

Sense organs disorders (Eye disorders, Ear and labyrinth disorders, taste):

Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been received. There have been reports of hearing loss with clarithromycin which is usually reversible on withdrawal of therapy. Tinnitus.

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

Psychiatric and nervous system disorders:

There have been reports of transient central nervous system side-effects including headache, dizziness, vertigo, anxiety, insomnia, bad dreams, confusion, disorientation, hallucinations, psychosis and depersonalisation. Convulsions have been reported rarely. Cardiac disorders:

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

Gastrointestinal disorders:

Nausea, dyspepsia, diarrhoea, vomiting, abdominal pain, paraesthesia, glossitis and tongue discolouration. There have been reports of tooth discolouration in patients treated with clarithromycin. Tooth discolouration is usually reversible with professional dental cleaning. Stomatitis has been reported.

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

Pancreatitis has been reported rarely.

Hepatobiliary disorders:

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.

Musculoskeletal and connective tissue disorders:

Arthralgia, myalgia.

Rhabdomyolysis can occur in rare cases during concomitant administration of clarithromycin and HMG-CoA reductase inhibitor, lovastatin and simvastatin.

Specific side effects have been observed in HIV patients treated for mycobacterial infections.

Renal and urinary disorders:

Cases of interstitial nephritis and renal failure have been reported rarely.

Increased investigations:

Increased serum creatinine, altered liver function tests.

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

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokaliemia and hypoxemia. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: macrolides

ATC-Code: J01FA09

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 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 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.

Mechanisms of resistance

Resistance of gram-positive organisms to the macrolides usually involves an alteration of the antimicrobial binding site. The MLS_B type of resistance, which may be constitutive or induced by exposure to certain macrolides in staphylococci and which is inducible in streptococci, is mediated by a variety of acquired genes (*erm* family) encoding methylases targeted at the peptidyl transferase centre of 23S ribosomal RNA. Methylation impedes binding of antibacterials to the ribosome and gives rise to cross-resistance to macrolides (all macrolides when constitutive), lincosamides and type B streptogramins but not to type A streptogramins. Less frequent mechanisms of resistance include antimicrobial degradation by inactivating enzymes such as esterase and active efflux of the antimicrobial from the bacteria.

Gram negative organisms may be intrinsically resistant to the macrolides because of the inability of the macrolide to effectively penetrate the outer cell membrane; macrolides having a better penetration may have activity against some gram-negative organisms.

Gram-negative organisms may also produce ribosomal methylase

Breakpoints

Breakpoint Concentrations

According to BSAC (January 2005) the following breakpoints have been defined for clarithromycin:

Organism	MIC Breakpoint Concentration (mg/L)	
	Susceptible ≤	Resistant >
Staphylococci	0.5	0.5
β-Haemolytic Streptococci*	0.5	0.5
<i>S.pneumoniae</i>	0.5	0.5
<i>M. catarrhalis</i> *	0.5	0.5
<i>H. influenzae</i> *	0.5	16**

* Active metabolite not taken into consideration

** Breakpoints for *H. influenzae*; strains with MICs below the low breakpoint are susceptible, those with MICs above the high breakpoint are resistant, others are intermediate

The following tentative MIC breakpoints have been defined for clarithromycin:
H. Pylori ≤ 1 mg/L susceptible, > 2 mg/L resistant.

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.

The susceptibility pattern of various micro-organisms to clarithromycin is presented below:

<i>Commonly susceptible species</i>
<u>Aerobic Gram-negative microorganisms</u> Moraxella catarrhalis
<u>Anaerobic microorganisms</u> Peptococcus species Peptostreptococcus species Propionibacterium acnes Clostridium perfringens
<u>Other microorganisms</u> Chlamydia pneumoniae Legionella pneumophila Mycoplasma pneumoniae
<i>Species for which acquired resistance may be a problem</i>
<u>Aerobic Gram-positive microorganisms</u> Staphylococcus aureus Staphylococcus aureus (methicillin-resistant)* Streptococcus agalactiae Streptococcus pneumoniae Streptococcus pyogenes
<u>Aerobic Gram-negative microorganisms</u> Haemophilus influenzae

*** Resistance to macrolides among MRSA is commonly more than 50% in the EU and affects nearly all strains in some areas.**

5.2 Pharmacokinetic properties

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Clarithromycin Tablets. The microbiologically active metabolite 14-hydroxyclearithromycin is formed by first pass metabolism. Clarithromycin Tablets may be given without regard to meals as food does not affect the extent of bioavailability of Clarithromycin Tablets. Food does slightly delay the onset of absorption of clarithromycin and formation of the 14-hydroxymetabolite. The pharmacokinetics of clarithromycin are non linear; however, steady-state is attained within 2 days of dosing. At 250 mg b.i.d. 15-20% of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36%). The 14-hydroxyclearithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces.

When clarithromycin 500 mg are given three times daily, the clarithromycin plasma concentrations are increased with respect to the 500 mg twice daily dosage.

Clarithromycin 250 mg Film Coated Tablets provide tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin is 80% bound to plasma proteins at therapeutic levels.

Clarithromycin Tablets also penetrates the gastric mucus. Levels of clarithromycin in gastric mucus and gastric tissue are higher when clarithromycin is co-administered with omeprazole than when clarithromycin is administered alone.

5.3 Preclinical safety data

In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5 g/kg BW).

In repeated dose studies, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys. At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400 mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.

Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and embryonic loss was seen in monkeys but only at dose levels which were clearly toxic to the mothers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Starch pregelatinised
Silicon dioxide
Povidone
Stearic acid
Magnesium stearate
Talc
Microcrystalline cellulose
Propylene glycol
Opadry OY-S32924.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pack sizes are 10, 12, 14, 20, 30, 50, 500 tablets in blister packs with outer pack and package leaflet.

All pack sizes may not be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Helm AG, Nordkanalstraße 28, D-20097 Hamburg

8 MARKETING AUTHORISATION NUMBER(S)

Clarithromycin 250mg Film Coated Tablets – PL20897/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/07/2008

10 DATE OF REVISION OF THE TEXT

11/07/2008

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 500 mg Film Coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clarithromycin 500 mg Film Coated Tablets: Clarithromycin 500 mg/tablet

For excipients see section 6.1.

3 PHARMACEUTICAL FORM

Clarithromycin 500 mg Film Coated Tablets:

A yellow coloured, elliptical, biconvex film-coated tablet with smooth surface containing 500 mg of clarithromycin.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarithromycin Tablets are indicated for treatment of infections caused by susceptible organisms. Indications include:

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

Upper respiratory tract infections for example, sinusitis and pharyngitis.

Clarithromycin Tablets are appropriate for initial therapy in community acquired respiratory infections and have been shown to be active in vitro against common and atypical respiratory pathogens as listed in section 5.1. "Pharmacodynamic properties".

Clarithromycin Tablets are also indicated in skin and soft tissue infections of mild to moderate severity.

Clarithromycin Tablets in the presence of acid suppression effected by omeprazole or lansoprazole are also indicated for the eradication of *H. pylori* in patients with duodenal ulcers.

See Dosage and Administration section.

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

4.2 **Posology and method of administration**

Patients with respiratory tract/skin and soft tissue infections

Adults: The usual dose is 250 mg twice daily for 7 days although this may be increased to 500 mg twice daily for up to 14 days in severe infections.

Children older than 12 years: As for adults.

Children younger than 12 years: Use an appropriate clarithromycin paediatric preparation.

Eradication of *H. pylori* in patients with duodenal ulcers (Adults)

Triple Therapy (7 - 14 days)

Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with amoxicillin 1000 mg twice daily for 7 - 14 days.

Triple Therapy (7 days)

Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with metronidazole 400 mg twice daily for 7 days.

Triple Therapy (7 days)

Clarithromycin 500 mg twice daily and omeprazole 40 mg daily should be given with amoxicillin 1000 mg twice daily or metronidazole 400 mg twice daily for 7 days.

Triple Therapy (10 days)

Clarithromycin 500 mg twice daily should be given with amoxicillin 1000 mg twice daily and omeprazole 20 mg daily for 10 days.

Dual Therapy (14 days)

The usual dose of clarithromycin is 500 mg three times daily for 14 days. Clarithromycin should be administered with oral omeprazole 40 mg once daily for 14 days.

Elderly: As for adults.

Renal impairment: Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance < 30 ml/min). If adjustment is necessary, the total daily dosage should be reduced by half, e.g. 250 mg once daily or 250 mg twice daily in more severe infections.

Clarithromycin Tablets may be given without regard to meals as food does not affect the extent of bioavailability.

4.3 Contraindications

Clarithromycin is contra-indicated in patients with known hypersensitivity to clarithromycin, other macrolide antibiotics or to any of the excipients in the tablet.

Clarithromycin and ergot derivatives must not be co-administered.

Concomitant administration of clarithromycin and any of the following drugs is contra-indicated: 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.

Clarithromycin is contra-indicated in patients with hypokaliemia. This may result in QT prolongation.

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 or 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.

H. pylori organisms may develop resistance to clarithromycin.

4.5 Interaction with other medicinal products and other forms of interaction

As with other macrolide antibiotics the use of clarithromycin in patients concurrently taking drugs metabolised by the cytochrome P 450 system (eg. warfarin, ergot alkaloids, triazolam, midazolam, disopyramide, lovastatin, rifabutin, phenytoin, valproate, cyclosporin, tacrolimus, rifampicin, cisapride, methyl prednisolone, vinblastine, sildenafil, hexobarbital, alfentanil, pimozide, terfenadine, alprazolam,

cilostazol and chinidin) may be associated with elevations in serum levels of these other drugs.

HMG-CoA reductase inhibitors:

Rhabdomyolysis, co-incident with the co-administration of clarithromycin, and HMG-CoA reductase inhibitors, such as lovastatin and simvastatin has been reported.

Further interactions:

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

As mentioned above 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.

The effects of digoxin may be potentiated with concomitant administration of Clarithromycin Tablets. 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 adult patients may result in decreased steady-state zidovudine levels. This can be largely avoided by staggering the doses of Clarithromycin Tablets and zidovudine by 1 - 2 hours. No such 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 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with $CL_{CR} < 30$ ml/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1g/day should not be co-administered with ritonavir.

Although the plasma concentrations of clarithromycin and omeprazole may be increased when they are administered concurrently, no adjustment to the dosage is necessary. At the dosages recommended, there is no clinically significant interaction between clarithromycin and lansoprazole. Increased plasma concentrations of clarithromycin may also occur when it is co-administered with aluminium oxide/magnesium hydroxide-antacids or ranitidine. No adjustment to the dosage is necessary.

Macrolides have been reported to have an effect on the metabolism of terfenadine/astemizole, in which case the terfenadine/astemizole values are elevated, which has, in individual cases, been shown to cause cardiac arrhythmias. Similar effects have also been reported with combined use of astemizole and other macrolides.

A concomitant administration of macrolide antibiotics with cyclosporine and bromocriptine may result in an increase of plasma levels of cyclosporine and bromocriptine. Consequently the dose of cyclosporine and bromocriptine needs to be decreased.

A potential cross-resistance of bacterial strains against clarithromycin and other macrolide antibiotics such as erythromycin and clindamycin needs to be considered. The concomitant administration of products belonging to this compound class is therefore not recommended.

There have been postmarketed reports of Torsade de Points 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

4.6 Pregnancy and lactation

The safety of clarithromycin during pregnancy and breast feeding of infants has not been established. Clarithromycin Tablets 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

Although clarithromycin is not expected to affect driving ability directly, side effects such as dizziness and vertigo may interfere with driving.

4.8 Undesirable effects

Infections and infestations:

Oral monilla, genital candidiasis

Blood and lymphatic system disorders:

Isolated cases of leukopenia and thrombocytopenia have been reported.

Immune system disorders:

Allergic reactions ranging from urticaria, mild skin eruptions and angioedema to anaphylaxis and rarely Stevens-Johnson syndrome / toxic epidermal necrolysis.

Metabolic disorders:

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

Sense organs disorders (Eye disorders, Ear and labyrinth disorders, taste):

Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been received. There have been reports of hearing loss with clarithromycin which is usually reversible on withdrawal of therapy. Tinnitus. There have been very rare reports of uveitis mainly in patients treated with concomitant rifabutin, most of these were reversible.

Psychiatric and nervous system disorders:

There have been reports of transient central nervous system side-effects including headache, dizziness, vertigo, anxiety, insomnia, bad dreams, confusion, disorientation, hallucinations, psychosis and depersonalisation. Convulsions have been reported rarely.

Cardiac disorders:

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

Gastrointestinal disorders:

Nausea, dyspepsia, diarrhoea, vomiting, abdominal pain, paraesthesia, glossitis and tongue discolouration. There have been reports of tooth discolouration in patients treated with clarithromycin. Tooth discolouration is usually reversible with professional dental cleaning. Stomatitis has been reported.

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

Pancreatitis has been reported rarely.

Hepatobiliary disorders:

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.

Musculoskeletal and connective tissue disorders:

Arthralgia, myalgia.

Rhabdomyolysis can occur in rare cases during concomitant administration of clarithromycin and HMG-CoA reductase inhibitor, lovastatin and simvastatin. Specific side effects have been observed in HIV patients treated for mycobacterial infections.

Renal and urinary disorders:

Cases of interstitial nephritis and renal failure have been reported rarely.

Increased investigations:

Increased serum creatinine, altered liver function tests.

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

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokaliemia and hypoxemia. Adverse reactions accompanying overdose 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: macrolides

ATC-Code: J01FA09

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 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 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.

Mechanism of resistance

Resistance of gram-positive organisms to the macrolides usually involves an alteration of the antimicrobial binding site. The MLS_B type of resistance, which may be constitutive or induced by exposure to certain macrolides in staphylococci and which is inducible in streptococci, is mediated by a variety of acquired genes (*erm* family) encoding methylases targeted at the peptidyl transferase centre of 23S ribosomal RNA. Methylation impedes binding of antibacterials to the ribosome and gives rise to cross-resistance to macrolides (all macrolides when constitutive), lincosamides and type B streptogramins but not to type A streptogramins. Less frequent mechanisms of resistance include antimicrobial degradation by inactivating enzymes such as esterase and active efflux of the antimicrobial from the bacteria.

Gram negative organisms may be intrinsically resistant to the macrolides because of the inability of the macrolide to effectively penetrate the outer cell membrane; macrolides having a better penetration may have activity against some gram-negative organisms.

Gram-negative organisms may also produce ribosomal methylase

Breakpoints

Breakpoint Concentrations

According to BSAC (January 2005) the following breakpoints have been defined for clarithromycin:

Organism	MIC Breakpoint Concentration (mg/L)	
	Susceptible \leq	Resistant \geq
Staphylococci	0.5	0.5
β -Haemolytic Streptococci*	0.5	0.5
<i>S. pneumoniae</i>	0.5	0.5
<i>M. catarrhalis</i> *	0.5	0.5
<i>H. influenzae</i> *	0.5	16**

* Active metabolite not taken into consideration

** Breakpoints for *H. influenzae*; strains with MICs below the low breakpoint are susceptible, those with MICs above the high breakpoint are resistant, others are intermediate

The following tentative MIC breakpoints have been defined for clarithromycin:
H. Pylori \leq 1 mg/L susceptible, $>$ 2 mg/L resistant.

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.

The susceptibility pattern of various micro-organisms to clarithromycin is presented below:

<i>Commonly susceptible species</i>
<u><i>Aerobic Gram-negative microorganisms</i></u> Moraxella catarrhalis
<u><i>Anaerobic microorganisms</i></u> Peptococcus species Peptostreptococcus species Propionibacterium acnes Clostridium perfringens
<u><i>Other microorganisms</i></u> Chlamydia pneumoniae Legionella pneumophila Mycoplasma pneumoniae
<i>Species for which acquired resistance may be a problem</i>
<u><i>Aerobic Gram-positive microorganisms</i></u> Staphylococcus aureus Staphylococcus aureus (<i>methicillin-resistant</i>)* Streptococcus agalactiae

Streptococcus pneumoniae
Streptococcus pyogenes
<u>Aerobic Gram-negative microorganisms</u>
Haemophilus influenzae

*** Resistance to macrolides among MRSA is commonly more than 50% in the EU and affects nearly all strains in some areas.**

5.2 Pharmacokinetic properties

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Clarithromycin Tablets. The microbiologically active metabolite 14-hydroxyclearithromycin is formed by first pass metabolism. Clarithromycin Tablets may be given without regard to meals as food does not affect the extent of bioavailability of Clarithromycin Tablets. Food does slightly delay the onset of absorption of clarithromycin and formation of the 14-hydroxymetabolite. The pharmacokinetics of clarithromycin are non linear; however, steady-state is attained within 2 days of dosing. At 250 mg b.i.d. 15-20% of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36%). The 14-hydroxyclearithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces.

When clarithromycin 500 mg are given three times daily, the clarithromycin plasma concentrations are increased with respect to the 500 mg twice daily dosage.

Clarithromycin 500 mg Film Coated Tablets provide tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin is 80% bound to plasma proteins at therapeutic levels.

Clarithromycin Tablets also penetrates the gastric mucus. Levels of clarithromycin in gastric mucus and gastric tissue are higher when clarithromycin is co-administered with omeprazole than when clarithromycin is administered alone.

5.3 Preclinical safety data

In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5 g/kg BW).

In repeated dose studies, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys. At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400 mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.

Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and embryonic loss was seen in monkeys but only at dose levels which were clearly toxic to the mothers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Starch pregelatinised
Silicon dioxide
Povidone
Stearic acid
Magnesium stearate
Talc
Microcrystalline cellulose
Propylene glycol
Opadry OY-S32924.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pack sizes are 10, 12, 14, 20, 30, 50, 500 tablets in blister packs with outer pack and package leaflet.

All pack sizes may not be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Helm AG, Nordkanalstraße 28, D-20097 Hamburg

8 MARKETING AUTHORISATION NUMBER(S)

Clarithromycin 500mg Film Coated Tablets – PL20897/0002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

11/07/2008

10 DATE OF REVISION OF THE TEXT

11/07/2008

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Clarithromycin 250mg film coated tablets Clarithromycin 500mg film coated tablets

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. **What Clarithromycin tablets are and what they are used for**
2. **Before you use Clarithromycin tablets**
3. **How to use Clarithromycin tablets**
4. **Possible side effects**
5. **How to store Clarithromycin tablets**

Clarithromycin 250mg and 500mg film-coated tablets

The name of your medicine is Clarithromycin 250mg film-coated tablets or Clarithromycin 500mg film-coated tablets (referred to as Clarithromycin tablets in this leaflet).

Each tablet contains 250mg or 500mg of clarithromycin as the active ingredient.

Other ingredients are: Croscarmellose sodium, starch pregelatinised, silicon dioxide, povidone, stearic acid, magnesium stearate, talc, microcrystalline cellulose, opadry OY-S 32924, polyethylene glycol.

Marketing authorisation holder and manufacturer:

The marketing authorisation holder and manufacturer is Helm AG, Nordkanalstrasse 28, D-20097 Hamburg.

1. WHAT CLARITHROMYCIN TABLETS ARE AND WHAT THEY ARE USED FOR

Clarithromycin Tablets are yellow, elliptical, biconvex film-coated tablets with a smooth surface.

Each pack contains 10, 12, 14, 20, 30, 50, or 500 tablets in blister packs.

Clarithromycin is an antibiotic belonging to a group of medicines known as the macrolides. Antibiotics stop the growth of bacteria that cause infections.

Clarithromycin tablets are used for the treatment of infections:

- Respiratory infections such as bronchitis and pneumonia
- Throat and sinus infections
- Skin and soft tissue infections
- Infections in patients with duodenal ulcer.

2. BEFORE YOU USE CLARITHROMYCIN TABLETS

Do not take Clarithromycin tablets:

- If you are hypersensitive (allergic) to clarithromycin, other macrolide antibiotics such as erythromycin or azithromycin, or to any of the ingredients in the tablets
- If you have low levels of potassium in your blood
- If you are taking ergotamine or dihydroergotamine tablets or use ergotamine inhalers for migraine. Consult your doctor for advice on alternative medicines.
- If you are taking terfenadine or astemizole (for hay fever or allergies) or are taking cisapride (for stomach disorders) or pimozide (for treatment of some mental conditions). Taking these medicines with Clarithromycin tablets can sometimes cause serious disturbances in heart rhythm. Consult your doctor for advice on alternative medicines
- If you are taking colchicine (usually taken for gout) as this can also cause serious side effects. Consult your doctor for advice on alternative medicines.

Take special care with Clarithromycin tablets:

- If you have any kidney or liver problems
- If you have used Clarithromycin before on several occasions or for a long time
- If they are to be taken by children under 12 years

Taking other medicines:

Clarithromycin may occasionally interfere with other medicines. It is important to tell your doctor or pharmacist if you are taking any of the following medicines:

- Theophylline (used to treat asthma). This may lead to increased side effects
- Warfarin (for thinning the blood), digoxin, quinidine or disopyramide (heart drug) or carbamazepine (for epilepsy). The effects of these medicines may be increased by Clarithromycin.
- Zidovudine (used in HIV patients). The effect may be reduced if given with Clarithromycin.
- Ritonavir (used in HIV patients).
- Omeprazole, antacids or ranitidine (used in stomach disorders). Terfenadine or astemizole (for hay fever or allergies). If given with Clarithromycin they may cause heart rhythm problems.
- Cyclosporin (used in organ transplants) or bromocriptine (for Parkinson's disease).
- Macrolide antibiotics such as erythromycin and clindamycin.
- Certain medicines that are broken down in the body in a similar way to clarithromycin. When taken with clarithromycin, their levels and therefore effects may be increased. These are ergotamine or dihydroergotamine (for migraine), triazolam, midazolam, alprazolam or hexobarbital (sedatives), disopyramide (heart drug), lovastatin or simvastatin (for high cholesterol), rifabutin or rifampicin (for treatment of some infections), phenytoin or valproate (for epilepsy), tacrolimus (used after organ transplants), cisapride (for stomach disorders), methyl prednisolone, vinblastine (for certain types of cancer), sildenafil (for impotence), alfentanil (general anaesthetic), pimozide (for treatment of some mental conditions), cilostazol (improves blood circulation in the legs), and quinidine.

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Pregnancy and Breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or breast-feeding do not take Clarithromycin tablets without consulting your doctor first.

Driving and using machines:

At the recommended doses, Clarithromycin is not known to affect the capacity to drive or use machines. However, you may experience dizziness or vertigo as a possible side effect. If affected you should not drive or operate machines.

3. HOW TO TAKE CLARITHROMYCIN TABLETS

Your doctor will tell you how to take Clarithromycin tablets and how long for. Do not stop taking Clarithromycin tablets early. It is important to take the tablets for as long as the doctor has told you to, otherwise the infection might come back.

The usual dose is:

For chest infections, soft tissue and skin infections:

Adults and children over 12 years: The usual dose is 250mg twice a day for 7 days. Your doctor may increase the dose to 500mg twice daily for up to 2 weeks, for severe infections

Children under 12 years: Use an appropriate Clarithromycin paediatric preparation.

For treatment of infection associated with duodenal ulcers:

Adults, including the elderly:

There are a number of effective treatment combinations available in which Clarithromycin Tablets are taken with one or two other medicines:

Triple Therapy (7-14 days)

Clarithromycin 500mg, lansoprazole 30mg and amoxicillin 1000mg, twice daily for 7 – 14 days.

Triple Therapy (7 days)

Clarithromycin 500mg, lansoprazole 30mg and metronidazole 400mg, twice daily for 7 days.

Triple Therapy (7 days)

Clarithromycin 500mg, omeprazole 40mg daily and amoxicillin 1000mg or metronidazole 400mg, twice daily for 7 days.

Triple Therapy (10 days)

Clarithromycin 500mg and amoxicillin 1000mg twice daily and omeprazole 20mg daily, for 10 days.

Dual Therapy (14 days)

The usual dose of Clarithromycin is 500mg three times daily with omeprazole 40mg once daily, for 14 days.

Patients with severe kidney problems:

The doctor may reduce the dose of Clarithromycin tablets.

Your doctor will decide which treatment combination is best for you. If you are unsure which tablets you should be taking or for how long, please ask your doctor for advice.

If you take more Clarithromycin tablets than you should

If you take more Clarithromycin tablets than you should, talk to a doctor or pharmacist immediately. An overdose is likely to cause vomiting or stomach pains.

Remember to take your medicine.

If you forget to take Clarithromycin tablets

If you forget to take Clarithromycin tablets do not take a double dose to make up for missed individual doses. Take one as soon as you remember and continue with the prescribed treatment as usual.

4. POSSIBLE SIDE EFFECTS

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

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

If any of the following happen, stop taking the tablets and tell your doctor immediately:

- You develop severe or prolonged diarrhoea, which may have blood or mucous in it, during or after taking Clarithromycin tablets
- You feel generally unwell or develop yellowing of the skin and /or eyes (jaundice), or have pale stools with dark urine.
- You have difficulty in breathing, fainting and swelling of the face and throat. You may have a serious allergic reaction and may need urgent medical attention.

Other side effects may occur, some of which could be severe, in which case tell your doctor immediately. These include:

- Feeling sick, vomiting, indigestion, pain, and diarrhoea
- Swelling of the mouth or tongue, thrush, tongue discolouration, and rarely tooth discolouration. Change in the sense of smell and taste can also occur.
- Skin rashes which may range in severity from mild itchy rash, swelling and skin eruptions to a rare condition called Stevens-Johnson reaction (severe illness with ulceration of the skin, mouth and eyes). Rarely a severe allergic reaction may occur causing fever and sloughing of the skin (toxic epidermal necrosis).
- Headache, dizziness, fear of heights, anxiety, difficulty sleeping, bad dreams, confusion, disorientation, hallucinations (seeing things), changes in mood or behaviour and change in sense of reality. Convulsions (fits) have been reported rarely.
- Hearing loss, 'ringing' in the ears.
- Changes in heart rhythm, inflammation of the kidneys, and kidney failure have been reported rarely
- A blood test may show an increase in liver enzymes. On rare occasions clarithromycin can cause liver and gall bladder problems. Very rarely liver failure can occur which may be fatal.
- Other side effects include muscle or joint pain, genital 'thrush', and low blood sugar. Low levels of white blood cells and inflammation of the pancreas have been reported rarely.
- Very rarely inflammation of the eye has been reported, usually in patients also taking rifabutin.

5. HOW TO STORE CLARITHROMYCIN TABLETS

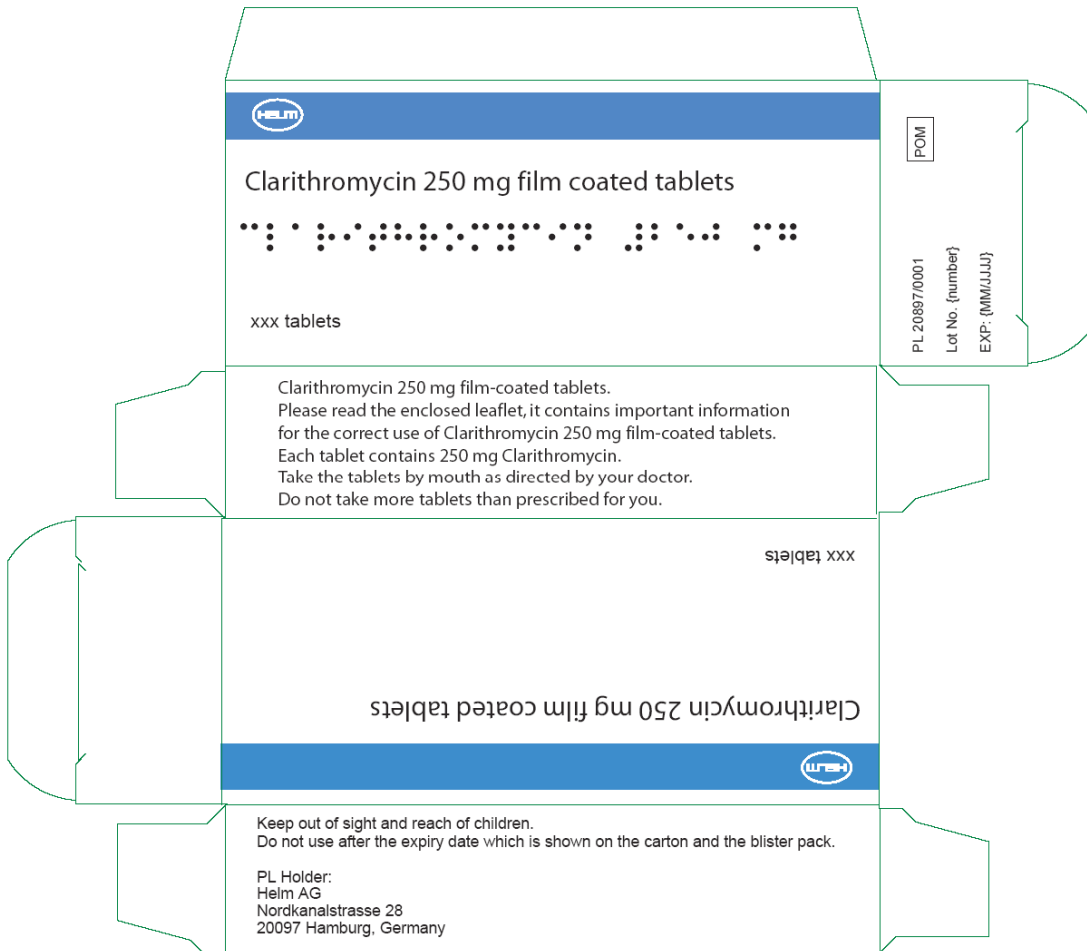
Keep Clarithromycin tablets out of reach and sight of children.

Do not use Clarithromycin tablets after the expiry date which is stated on the pack.

This leaflet was prepared in January 2007 Leaflet approved: MM/YYYY

PACKAGING

250 mg tablet carton:



500 mg tablet carton:

