1.6 PRODUCT INFORMATION

1.6.1 PRESCRIBING INFORMATION (SUMMARY OF PRODUCT CHARACTERISTICS)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

CLARYL-500 [Clarithromycin Tablets USP 500 mg]
Strength **:** 500 mg
Pharmaceutical Form **:** Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Clarithromycin USP ……. 500 mg
Excipients .....…… q.s.
Colour: Aluminium lake of Quinoline yellow W.S.

3. PHARMACEUTICAL FORM

Film-coated tablet

Yellow coloured oblong, biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Clarithromycin tablets are indicated in adults and children 12 years and older.(Adult only formulations, e.g. tablets, IV)

Clarithromycin is indicated in children, 6 months to 12 years. (paediatric Oral suspension).

Clarithromycin Tablets are indicated for treatment of the following infections caused by susceptible organisms:

Lower respiratory tract infections for example: acute and chronic bronchitis, and pneumonia.
Upper respiratory tract infections for example: sinusitis and pharyngitis.

Clarithromycin is appropriate for initial therapy in community acquired respiratory infections and has been shown to be active in vitro against common and atypical respiratory pathogens as listed in the microbiology section.

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

Clarithromycin in the presence of acid suppression effected by omeprazole or lansoprazole is also indicated for the eradication of *H. pylori* in patients with duodenal ulcers. See Dosage and Administration section.

Clarithromycin is usually active against the following organisms in vitro:

Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A beta-hemolytic streptococci); alpha-hemolytic streptococci (viridans group); *Streptococcus (Diplococcus) pneumoniae; Streptococcus agalactiae; Listeria monocytogenes*.

Gram-negative Bacteria: *Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae; Legionella pneumophila; Bordetella pertussis; Helicobacter pylori; Campylobacter jejuni.*

Mycoplasma: *Mycoplasma pneumoniae; Ureaplasma urealyticum.*

Other Organisms: *Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae*

Anaerobes: Macrolide-*susceptible Bacteroides fragilis; Clostridium perfringens*; Peptococcus species; Peptostreptococcus species; *Propionibacterium acnes*.

Clarithromycin has bactericidal activity against several bacterial strains. The organisms include *Haemophilus influenzae; Streptococcus pneumoniae; Streptococcus pyogenes; Streptococcus agalactiae; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae; H. pylori* and *Campylobacter spp*.

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

4.2 Posology and method of administration

Posology:
The dosage of Clarithromycin film-coated tablets depends on the type and severity of the infection and has to be defined in any case by the physician.

Adults:
• Standard dosage: The usual dose is 250mg twice daily (in the morning and in the evening)

• High dosage treatment (severe infections): The usual dose may be increased to 500 mg twice daily in severe infections.

Children older than 12 years: As for adults.

Children younger than 12 years: Use of Clarithromycin 250mg Tablets are not recommended for children younger than 12 years. Use Clarithromycin Paediatric Suspension.

Eradication of Helicobacter pylori in adults:
In patients with gastro-duodenal ulcers due to Helicobacter pylori infection Clarithromycin is given in a dosage of 500 mg twice daily. The national recommendations for Helicobacter pylori eradication have to be considered.

Duration of therapy:
The duration of therapy with Clarithromycin depends on the type and severity of the infection.
The usual duration of treatment is 7 to 14 days.

Dosage in renal functional impairment:
Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance < 30 ml/min (<0.5 ml/s)). If adjustment of dose is necessary, the total daily dosage should be reduced by half.

The duration of treatment should not exceed 14 days in these patients.

Patients with hepatic impairment:
Caution should be exercised when administrating clarithromycin in patients with hepatic impairment.

Method of administration:
The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water).
Clarithromycin may be given irrespective of food intake.

4.3 Contraindications

• Clarithromycin is contra-indicated 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.

• 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.
• Concomitant administration with simvastatine is contraindicated.
• Clarithromycin should not be administered to hypokalaemic patients (prolongation of QT-time.

4.4 Special warnings and special 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. 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.

• 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.

• Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these medicinal products.

• 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.
Contains lactose, Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other FPPs and other forms of interaction

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

<u>Cisapride, pimozide, terfenadine and astemizole</u>
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.

<u>Ergotamine/dihydroergotamine</u>
Post-marketing reports indicate that coadministration 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.

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 (fluconazol, itraconazol, ketoconazol) increases the risk of cardial toxicity (prolonged QT-interval, Torsades des Pointes, cardiac arrest).

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 (C_{min}) 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 C_{max}, C_{min} 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. Coadministration 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 coadministered 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 reductase 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.

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(R)-hydroxyclarithromycin, 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 Preclinical safety data). 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.

Fertility:
Data from animal studies have shown no adverse effects on fertility. The risk for humans is unknown (see Preclinical safety data).

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.

Musculoskeletal 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.

After taking this product, some cases of granulocytopenia have occurred; these symptoms disappear after stopping the treatment.

4.9 Overdose

Symptoms of intoxification:
Reports indicate that the ingestion of large amounts of clarithromycin 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, hypokaliaemia and hypoxaemia.

Therapy of intoxification:
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

Pharamacotherapeutic group: Macrolides,

ATC Code: J01FA09

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 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, 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 staphyllococci 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)*

		Species-related breakpoints (S≤/R>)														Non-species related break-points[A] S≤/R>
		Enterobacteriaceae	*Pseudomonas*	*Acinetobacter*	*Staphylococcus*	*Enterococcus*	*Streptococcus A,B,C,G*	*S.pneumoniae*	*Other streptococci*	*Hinfluenzae*	*M.catarr-halis*	*Ngonorrhoeae*	*Nmeningitidis*	*Gram-negative anaerobes*	*Gram-positive anaerobes*	
Clarithromycin[B,C]	RD	--	--	--	1/2	--	0.25/ 0.5	0.25/ 0.5	IE	1/32[D]	0.25/ 0.5	--	--	--	--	IE

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, lincosamines 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 prevalance of resistance is such that the utility of the agent in atleast some types of infections is questionable.

Commonly susceptible species
Aerobic, Gram-positive microorganisms
Streptococcus group F
Corynebacterium diptheriae
Aerobic, Gram-negative microorganisms

Bordetella pertusis
Moraxella catarrhalis
Pasteurella multocida
Legionella spp.
Anaerobic microorganisms
Clostridium spp., other than *C. difficile*
Other microorganisms
Mycoplasma pneumoniae
Chlamydia trachomatis
Clamydophila pneumoniae
Clamydophilapsitacci
Mycobacterium spp.
Species for which acquired resistance may be a problem#
Aerobic, Gram-positive microorganisms
Streptococcus group A*, C, G
Streptococcus group B
Streptococcus viridans
Enterococcus spp^{+}
Staphylococcus aureus, methicillin-susceptible and methicillin-resistant+
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
Enterobacteriacea
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

Absorption:
Clarithromycin is rapidly and well absorbed from the gastrointestinal tract – primarily in the jejunum – but undergoes extensive first-pass metabolism after oral administration. The absolute bioavailability of a 250-mg clarithromycin tablet is approximately 50%. Food slightly delays the absorption but does not affect the extent of bioavailability. Therefore, clarithromycin tablets may be given without regard to food. Due to its chemical structure (6-O-Methylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. Peak plasma levels of 1 – 2 µg/ml clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily the peak plasma level was 2.8 µg/ml.

After administration of 250 mg clarithromycin twice daily the microbiologically active 14-hydroxy metabolite attains peak plasma concentrations of 0.6 µg/ml. Steady state is attained within 2 days of dosing.

Distribution:
Clarithromycin penetrates well into different compartments, with an estimated volume of distribution of 200-400 L. Clarithromycin provides concentrations in some tissues that are several times higher than the circulating level of the active substance. Increased levels have been found in both tonsils and lung tissue. Clarithromycin also penetrates the gastric mucus.
Clarithromycin is approximately 70% bound to plasma proteins at therapeutic levels.

Biotransformation and elimination:
Clarithromycin is rapidly and extensively metabolised in the liver. Metabolism is in the liver involving the P450 cytochrome system. Three metabolites are described: N-demethyl clarithromycin, decladinosyl clarithromycin and 14-hydroxy clarithromycin.

The pharmacokinetics of clarithromycin is non-linear due to saturation of hepatic metabolism at high doses. Elimination half-life increased from 2-4 hours following administration of 250 mg clarithromycin twice daily to 5 hours following administration of 500 mg clarithromycin twice daily. The half-life of the active 14-hydroxy metabolite ranges between 5 to 6 hours following administration of 250 mg clarithromycin twice daily.

Approximately 20 -40% of clarithromycin is excreted as the unchanged active substance in the urine. This proportion is increased when the dose is increased. An additional 10% to 15% is excreted in the urine as 14-hydroxy metabolite. The rest is excreted in the faeces. Renal insufficiency increases clarithromycin levels in plasma, if the dose is not decreased.

Total plasma clearance has been estimated to approximately 700 ml/min (11.7 ml/s), with a renal clearance of approximately 170 ml/min (2.8 ml/s).

Special Populations:
Renal impairment: Reduced renal insufficiency function results in increased plasma levels of clarithromycin and the active metabolite levels in plasma.

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%).

Fertility and reproduction studies have shown that daily doses of 150 to 160mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats at 150mg/kg/day were 2-fold higher than that observed in humans.
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

Colloidal Silicon Dioxide
Microcrystalline Cellulose
Starch
P.V.P.K. 30
Isopropyl Alcohol
Magnesium Stearate
Cross-Carmellose Sodium [AC-DI-SOL]
Talc
Sodium starch glycolate
Stearic acid
Methylene chloride
Wincoat WT-1125 A1 Lake and Quanoline

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 Months

6.4 Special precautions for storage
Do not store above 30°C. No special precautions for storage

6.5 Nature and contents of container

ALU ALU blister

Pack sizes: 1 x 10s blister,

10 blisters are packed in one printed carton with pack insert.

6.6 Instructions for use and handling and disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

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20/07/2016