GP CLARITHROMYCIN XR TABLET 500MG

COMPOSITION:
Each film coated extended-release tablet contains
Clarithromycin Citrate equivalent to Clarithromycin 500mg

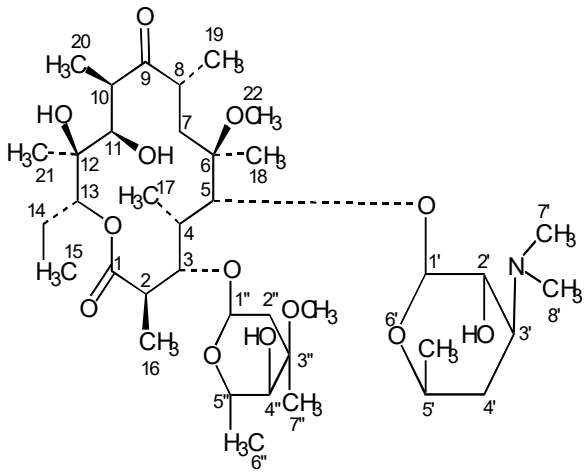
LIST OF EXCIPIENTS:
Tablet core
Lactose Monohydrate, Hydroxypropyl methylcellulose, Purified Water, Hydroxypropyl methyl cellulose phthalate, Purified Talc and Magnesium Stearate

Film Coat
Opadry II Yellow 31G52300 (consist of Hypromellose, Lactose Monohydrate, Titanium Dioxide, Polyethylene Glycol, Talc and Quinoline Yellow Aluminium Lake) and Purified Water

PRESENTATION:
Blisters composed of Rigid PVC film coated with PVdC Pharma Grade and Printed Aluminium foil.
Blister packs are supplied in cartons of 5, 7, 10, 50, 70 or 100 tablets.

PRODUCT DESCRIPTION:
Yellow colored, film coated, oblong shaped, biconvex tablet, with both sides plain.

PROPERTIES:
Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-0-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. The structural formula is



CLINICAL PHARMACOLOGY:
PHARMACODYNAMICS:

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide
ATC-Code: J01FA09

Clarithromycin is a semi-synthetic macrolide antibiotic obtained by substitution of a CH3O group for the hydroxyl (OH) group at position 6 of the erythromycin lactonic ring.

Specifically clarithromycin is 6-O-methyl erythromycin A. The white to off-white antibiotic powder is bitter, practically odorless, essentially insoluble in water, and slightly soluble in ethanol, methanol, and acetonitrile. Its molecular weight is 747.96.

A study in community acquired pneumonia investigated the effect of clarithromycin vs amoxicillin on plasma concentrations of IL-6, IFNγ and IL-10 before starting therapy [1st day] and at the 3rd and 7th days of therapy. Twenty-three patients received clarithromycin orally 500mg b.i.d for 7 days, clarithromycin significantly decreased plasma levels of IL-6 (ng/ml) [pro-inflammatory cytokine] at 3rd day (1.70± 0.73) and 7thday (1.06± 0.39) compared to basal value (2.22 ± 0.82) and significantly increased those of IFNγ (pg/ml) [anti-inflammatory cytokine] at the 3rd (8.92 ± 3.59) and 7th day (10.06 ± 3.90) compared to basal value (6.10 ± 2.64) and IL-10 [anti-inflammatory cytokine] at 3rd day (11.1 ± 3.62) and 7th day (14.92 ± 5.11) in comparison to basal level (6.95 ± 2.84).

Microbiology
Clarithromycin exerts its anti-bacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. Clarithromycin has demonstrated excellent *in vitro* activity against both standard strains of bacteria and clinical isolates. 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 one-$\log_2$ dilution more potent than the MICs of erythromycin. *In vitro* data also indicate Clarithromycin has excellent activity against *Legionella pneumophila*, and *Mycoplasma pneumonia*. It is bactericidal to *Helicobacter pylori*; this activity of clarithromycin is greater at neutral pH than at acid pH. *In vitro* and *In vivo* data show this antibiotic has activity against clinical significant mycobacterial species. The *in vitro* data indicate *Enterobacteriaceae*, pseudomonas species and other non-lactose fermenting Gram-negative bacilli are not susceptible to clarithromycin.

Clarithromycin has been shown to be active against most strains of the following micro-organisms both *in vitro* and in clinical infections:

Aerobic Gram-Positive microorganisms
Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes
Listeria monocytogenes

Aerobic Gram-negative microorganisms
Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Legionella pneumophila

Other microorganisms
Mycoplasma pneumoniae
Chlamydia pneumoniae (TWAR)

Mycobacteria
Mycobacterium leprae
Mycobacterium kansasii
Mycobacterium chelonae
Mycobacterium fortuitum
Mycobacterium avium complex (MAC) consisting of: *Mycobacterium avium*
Mycobacterium Intracellulare

Beta-lactamase production should have no effect on clarithromycin activity.
NOTE: Most strains of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.

Helicobacter
Helicobacter pylori
In cultures performed prior to therapy, *H. pylori* was isolated and clarithromycin MIC's were determined pre-treatment in 104 patients. Of these, four patients had resistant strains, two patients had strains with intermediate susceptibility, and 98 patients had susceptible strains.

The following *in vitro* data are available, **but their clinical significance is unknown**. Clarithromycin exhibits *in vitro* activity against most strains of the following microorganisms; however, the safety and effectiveness of clarithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms
Streptococcus agalactiae
Streptococci (Group C,F,G)
Viridans group streptococci

Aerobic Gram-negative microorganisms
Bordetella pertussis
Pasteurella multocida

Anaerobic Gram-positive microorganisms
Clostridium perfringens
Peptococcus niger
Propionibacterium acnes

Anaerobic Gram-negative microorganisms
Bacteroides melaninogenicus

Spirochetes
Borrelia burgdorferi
Treponema pallidum

Campylobacter
Campylobacter jejuni

The principal metabolite of clarithromycin in man and other primates is a microbiologically-active metabolite, 14-hydroxy (OH)-clarithromycin. This metabolite is active or 1-to-2 fold less active than the parent compound for most organisms, except for *H. influenzae* against which it is twice as active. The parent compound and the 14-OH metabolite exert either an additive or synergistic effect on *H. influenzae in vitro* and *in vivo*, depending on bacterial strains.

Clarithromycin was found to be two to ten times more active than erythromycin in several experimental animal infection models. It was shown, for example, to be more effective than erythromycin in mouse systemic infection, mouse subcutaneous abscess, and mouse respiratory tract infections caused by *S. pneumoniae*, *S. aureus*, *S. pyogenes*, and *H. influenzae*. In guinea pigs with Legionella infection this effect was more pronounced; an intraperitoneal dose of 1.6 mg/kg/day of clarithromycin was more effective than 50 mg/kg/day of erythromycin.

Susceptibility Tests
Quantitative methods that require measurement of zone diameters give the most precise estimates of susceptibility of bacteria to antimicrobial agents. One recommended procedure uses discs impregnated with 15 µg of clarithromycin for testing susceptibility (Kirby-Bauer diffusion test); interpretations correlate inhibition zone diameters of this disc test with MIC values for clarithromycin. The MIC's are determined by the broth or agar dilution method.

With these procedures, a report from the laboratory of "susceptible" indicates the infecting organism is likely to respond to therapy. A report of "resistant" indicates the infective organism is not likely to respond to therapy. A report of "Intermediate Susceptibility" suggests the therapeutic effect of the drug may be equivocal or the organism would be susceptible if higher doses were used. (Intermediate susceptibility is also referred to as moderately susceptible.)

PHARMACOKINETICS AND DRUG METABOLISM:

Absorption

The kinetics of orally administered modified-release clarithromycin have been studied in adult humans and compared with clarithromycin 250mg and 500mg immediate release tablets. The extent of absorption was found to be equivalent when equal total daily doses were administered, with the Extended Release (ER) tablets taken with food. The absolute bioavailability is approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing. Based upon the finding of equivalent absorption the following *in vitro* and *in vivo* data are applicable to the modified-release formulation. Concomitant food intake increases the exposure to clarithromycin. Therefore, clarithromycin ER tablets should be taken with food.

Distribution, Biotransformation and Elimination

In vitro: In vitro studies showed the protein binding of clarithromycin in human plasma averaged about 70% at concentrations of 0.45 - 4.5µg/mL. A decrease in binding to 41% at 45.0µg/mL suggested the binding sites might become saturated, but this only occurred at concentrations far in excess of therapeutic drug levels.

In vivo: Results of animal studies showed clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were found in the liver and lung where the tissue to plasma (T/P) ratios reached 10 to 20.

Normal Subjects

In fed patients given 500 mg clarithromycin ER once-daily, the peak steady state plasma concentration of clarithromycin and 14-OH-clarithromycin were 1.3 and 0.48 mcg/mL, respectively. Elimination half-lives of the parent drug and metabolite were approximately 5.3 hours and 7.7 hours, respectively. When clarithromycin ER 1000 mg once-daily (2 x 500 mg) was administered, the steady state C_{max} for clarithromycin and its hydroxylated metabolite averaged 2.4 mcg/mL and 0.67 mcg/mL, respectively. The half-life of the parent drug at the 1000 mg dose level was approximately 5.8 hours, while that of the 14-OH-clarithromycin was approximately 8.9 hours. The T_{max} for both the 500 mg and 1000 mg doses was approximately six hours. At steady state the 14-OH-clarithromycin levels did not increase proportionately with the clarithromycin dose, and the apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at the higher doses. This non-linear pharmacokinetic behavior of clarithromycin, coupled with the overall decrease in the formation of 14-hydroxylation and N-demethylation products at the higher doses, indicates the non-linear metabolism of clarithromycin becomes more pronounced at high doses.

Urinary excretion accounted for approximately 40% of the clarithromycin dose. Faecal elimination accounts for approximately 30%.

Patients

Clarithromycin and its 14-OH metabolite distribute readily into body tissues and fluids. Limited data from a small number of patients suggests clarithromycin does not achieve significant levels in cerebrospinal fluid after oral doses (i.e., only 1 to 2% of serum levels in CSF in patients with normal blood-CSF barriers). Concentrations in tissues are usually several fold higher than serum concentrations.

Hepatic Impairment

In a study comparing one group of healthy human subjects with a group of subjects with liver impairment who were given 250mg of clarithromycin immediate release b.i.d for two days and a single 250mg dose the third day, steady state plasma levels and systemic clearing of clarithromycin were not significantly different between the two groups.

In contrast, steady state concentrations of the 14-OH metabolite were markedly lower in the group of hepatic-impaired subjects. This decreased metabolic clearance of the parent compound by 14-hydroxylation was partially offset by an increase in the renal clearance of parent drug, resulting in comparable steady state levels of parent drug in the hepatic impaired and healthy subjects. These results indicate no adjustment of dosage is necessary for subjects with moderate or severe hepatic impairment but with normal renal function.

Renal Impairment
A study was conducted to evaluate and compare the pharmacokinetic profile of multiple 500 mg oral doses of clarithromycin immediate release in subjects with normal and decreased renal function. The plasma levels, half-life, C_{max} and C_{min} for both clarithromycin and its 14-OH metabolite were higher and AUC was larger in subjects with renal impairment. K_{elim} and urinary excretion were lower. The extent to which these parameters differed was correlated with the degree of renal impairment; the more severe the renal impairment, the more significant the difference.

Elderly Subjects
A study was also conducted to evaluate and compare the safety and pharmacokinetic profiles of multiple 500 mg oral doses of clarithromycin immediate release in healthy elderly male and female subjects to those in healthy young adult male subjects. In the elderly group, circulating plasma levels were higher and elimination slower than in the younger group for both parent drug and 14-OH metabolite. However, there was no difference between the two groups when renal clearance was correlated with creatinine clearance. It is concluded from those results that any effect on the handling of clarithromycin is related to renal function and not to age per se.

INDICATIONS & USAGE:
Clarithromycin Extended-Release Tablets USP is indicated for treatment of infections caused by susceptible organisms. Indications include:

Lower respiratory tract infections for example, acute and chronic bronchitis, and pneumonia (see section special warnings and clinical pharmacology regarding Sensitivity Testing).

Upper respiratory tract infections for example, sinusitis and pharyngitis.

Clarithromycin Extended-Release Tablets USP is also indicated in skin and soft tissue infections of mild to moderate severity, for example folliculitis, cellulitis and erysipelas (see section special warnings and clinical pharmacology regarding Sensitivity Testing).

DOSAGE & ADMINISTRATION:
Adults: The usual recommended dosage of Clarithromycin Extended-Release Tablets USP in adults is one 500 mg extended release tablet daily to be taken with food. In most severe infections, the dosage can be increased to two 500 mg extended release tablets daily. The usual duration of treatment is 7 to 14 days.

Children older than 12 years: As for adults.

Children younger than 12 years: The use of Clarithromycin Extended-Release Tablets USP has not been studied in children less than 12 years of age.

Clarithromycin Extended-Release Tablets USP should not be used in patients with renal impairment (creatinine clearance less than 30 mL/min). Clarithromycin immediate release tablets may be used in this patient population (see section Contraindication).

Do not crush or chew Clarithromycin Extended-Release Tablets USP.

Renal Impairment

Clarithromycin extended release should not be used in patients with significant renal impairment (creatinine clearance less than 30 ml/min), as appropriate clarithromycin dosage reduction is not possible when administering this product. Clarithromycin immediate release tablets may be utilized in this patient population. Refer the dosing for immediate release formulation.

SIDE EFFECTS:

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and pediatric populations are abdominal pain, diarrhea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.

There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without preexisting mycobacterial infections.

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with Clarithromycin Extended-Release formulation.

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

Adverse Reactions Reported with Clarithromycin				
MedDRA System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Not Known* (cannot be estimated from the available data)**
Infections and infestations			Cellulitis[1], candidiasis, gastroenteritis[2],infection[3], vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system disorders			Leukopenia, neutropenia[4], thrombocythemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune System disorders			Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness[3], screaming[3]	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache, taste perversion	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence, tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest[1], atrial	Torsade de pointes,

			fibrillation[1], electrocardiogram QT prolonged, extrasystoles[1], palpitations	ventricular tachycardia, ventricular fibrillation
Vascular disorders		Vasodilation[1]		Hemorrhage
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	
Gastrointestinal disorders		Diarrhea, vomiting, dyspepsia, nausea, abdominal pain	Esophagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence.	Pancreatitis acute, tongue discolouration, tooth discoloration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased[4]	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous[1], pruritus, urticaria, rash maculopapular[3]	Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne, Henoch-Schonlein purpura
Musculoskeletal and connective tissue disorders			Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2]**, myopathy
Renal and urinary disorders			Blood creatinine increased[1], blood urea increased[1]	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	
Investigations			Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio increased, prothrombin time prolonged, urine color abnormal
* Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.				

**In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with other drugs known to be associated with rhabdomyolysis (such as statins, fibrates, colchicine or allopurinol).
[1] ADRs reported only for the Powder for Solution for Injection formulation
[2]ADRs reported only for the Extended-Release Tablets formulation
[3] ADRs reported only for the Granules for Oral Suspension formulation
[4] ADRs reported only for the Immediate-Release Tablets formulation

Immunocompromised Patients
In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of HIV disease or intercurrent illness.

In adult patients, the most frequently reported adverse events by patients treated with total daily doses of 1000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhea, rash, flatulence, headache, constipation, hearing disturbance, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT) elevations. Additional low-frequency events included dyspnea, insomnia, and dry mouth.

In these immunocompromised patients evaluations of laboratory values were made by analyzing those values outside the seriously abnormal level (i.e., the extreme high or low limit) for the specified test. On the basis of this criteria, about 2 to 3% of these patients who received 1000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients also had elevated BUN levels.

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

Cisapride, pimozide, astemizole and terfenadine
Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and *torsades de pointes*. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly.

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and *torsades de pointes*. In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a two to three fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergot alkaloids
Postmarketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids is contraindicated.

Oral Midazolam
When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and clarithromycin is contraindicated.

HMG-CoA Reductase Inhibitors (statins)
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.
Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g.fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

Lomitapide
Concomitant administration of clarithromycin with lomitapide is contraindicated due to the potential for markedly increased transaminases.

Effects of Other Medicinal Products on Clarithromycin

Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Because of the potential for a similar risk with other macrolides when used in combination with hydroxychloroquine or chloroquine, careful consideration should be given to the balance of benefits and risks before prescribing clarithromycin for any patients taking hydroxychloroquine or chloroquine.

Drugs that are inducers of CYP3A (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inducer administered).

Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

The following drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine
Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-OH-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Etravirine
Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.

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-OH-

clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. 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 CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 gm/day should not be coadministered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see section below, **Bidirectional drug interactions**).

Effect of Clarithromycin on Other Medicinal Products

Antiarrhythmics

There have been postmarketed reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during co-administration of clarithromycin with these drugs. Serum levels of these medications should be monitored during clarithromycin therapy.

There have been post marketing reports of hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Oral hypoglycemic agents/Insulin

With certain hypoglycemic drugs such as pioglitazone, rosiglitazone, nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose is recommended.

CYP3A-based Interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g., carbamazepine) and/or the substrate is extensively metabolized by this enzyme. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g., warfarin, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Direct acting oral anticoagulants (DOACs)

The DOAC dabigatran is a substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolized via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding.

Omeprazole
Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (Cmax, AUC0-24, and t1/2 increased by 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

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

Theophylline, carbamazepine
Results of clinical studies indicate there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these drugs was administered concomitantly with clarithromycin.

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.

Triazolobenzodiazepines (e.g. alprazolam, midazolam, triazolam)
When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other Drug Interactions
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. Concomitant use of clarithromycin and colchicine is contraindicated.

Digoxin
Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine. This interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. Similar interaction studies with clarithromycin modified release and zidovudine have not been conducted.

Phenytoin and Valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs metabolized by cytochrome P450 isoforms other than CYP3A (e.g., phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

Bi-directional Drug 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-OH-clarithromycin, 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. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

Calcium Channel Blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

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 bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg bid) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state AUC and C_{max} values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} 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 performed with saquinavir alone 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.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy.

Long-term use may, as with other antibiotics, result in colonization with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

Caution is advised in patients with severe renal insufficiency.

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of C.difficile. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Clarithromycin is principally metabolized by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

Colchicine
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. Concomitant administration of clarithromycin and colchicine is contraindicated.

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam.

Cardiovascular Events
Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in treatment with macrolides including clarithromycin. Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including *torsades de pointes),* clarithromycin should be used with caution in the following patients;

• Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia
• Clarithromycin must not be given to patients with hypokalaemia or hypomagnesaemia.
• Patients concomitantly taking other medicinal products associated with QT prolongation.
• Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia.
• Patients currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III; antipsychotic agents; antidepressants; fluoroquinolones; or others
• Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval

Carefully consider the balance of benefits and risks before prescribing clarithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see Drug Interactions section).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

Pneumonia

In view of the emerging resistance of Streptococcus pneumoniae to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Skin and soft tissue infections of mild to moderate severity

These infections are most often caused by Staphylococcus aureus and Streptococcus pyogenes, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where beta–lactam antibiotics cannot be used (e.g., allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium minutissimum*, acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, DRESS, and Henoch-Schonlein purpura, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme.

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

HMG-CoA Reductase Inhibitors (statins):

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated. Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathyIn situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered.

Oral Hypoglycemic Agents/Insulin

The concomitant use of clarithromycin and oral hypoglycemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycemia. Careful monitoring of glucose is recommended.

Oral Anticoagulants

There is a risk of serious hemorrhage and significant elevations in INR and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding.

Excipients
Clarithromycin Modified Release tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take these medicines.

Preclinical Safety Data
Acute, Sub-chronic, and Chronic Toxicity
Studies were conducted in mice, rats, dogs and/or monkeys with clarithromycin administered orally. The duration of administration ranged from a single oral dose to repeated daily oral administration for six consecutive months.

In acute mouse and rat studies, one rat, but no mice, died following a single gavage of 5 g/kg body weight. The median lethal dose, therefore, was greater than 5 g/kg, the highest feasible dose for administration.

No adverse effects were attributed to clarithromycin in primates exposed to 100 mg/kg/day for 14 consecutive days or to 35 mg/kg/day for one month. Similarly, no adverse effects were seen in rats exposed to 75 mg/kg/day for one month, to 35 mg/kg/day for three months, or to 8 mg/kg/day for six months. Dogs were more sensitive to clarithromycin, tolerating 50 mg/kg/day for 14 days, 10 mg/kg/day for one and three months, and 4 mg/kg/day for six months without adverse effects.

The major clinical signs at toxic doses in these studies described above included emesis, weakness, reduced food consumption and reduced weight gain, salivation, dehydration, and hyperactivity. Two of ten monkeys receiving 400 mg/kg/day died on treatment day eight; yellow discolored feces were passed on a few isolated occasions by some surviving monkeys given a dose of 400 mg/kg/day for 28 days.

The primary target organ at toxic dosages in all species was the liver. The development of hepatotoxicity in all species was detectable by early elevation of serum concentrations of alkaline phosphatase, alanine and aspartate aminotransferase, gamma-glutamyl transferase, and/or lactic dehydrogenase. Discontinuation of the drug generally resulted in a return to or toward normal concentrations of these specific parameters.

Additional tissues less commonly affected in the various studies included the stomach, thymus and other lymphoid tissues, and the kidneys. Conjunctival injection and lacrimation, following near therapeutic dosages, occurred in dogs only. At a massive dosage of 400 mg/kg/day, some dogs and monkeys developed corneal opacities and/or edema.

Fertility, Reproduction, and Teratogenicity
Fertility and reproduction studies in female rats have shown that daily dosages of 150 mg/kg/day (highest dose tested) caused no adverse effects on the estrous cycle, fertility, parturition, and number and viability of offspring. In male rats, there was no evidence of adverse toxicity on fertility up to 250mg/kg. Two teratogenicity studies in both Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.) rats, one study in New Zealand White rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. Only in one additional study in Sprague-Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (approximately 6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony. Two studies in mice also revealed a variable incidence of cleft palate (3 to 30%) following doses of 70 times the upper range of the usual daily human clinical dose (500 mg b.i.d.), but not at 35 times the maximal daily human clinical dose, suggesting maternal and fetal toxicity but not teratogenicity.

Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately ten times the upper range of the usual daily human dose (500 mg b.i.d.), starting at gestation day 20. This effect has been attributed to maternal toxicity of the drug at very high doses. An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the maximal intended daily dosage produced no unique hazard to the conceptus.

A dominant lethal test in mice given 1000 mg/kg/day (approximately 70 times the maximal human daily clinical dose) was clearly negative for any mutagenic activity, and, in a Segment I study of rats treated with up to 500 mg/kg/day (approximately 35 times the maximal daily human clinical dose) for 80 days, no evidence of functional impairment of male fertility due to this long-term exposure to these very high doses of clarithromycin was exhibited.

Mutagenicity
Studies to evaluate the mutagenic potential of clarithromycin were performed using both non-activated and rat-liver-microsome-activated test systems (Ames Test). Results of these studies provided no evidence of mutagenic potential at drug concentrations of 25 mcg/Petri plate or less. At a concentration of 50 mcg the drug was toxic for all strains tested.

PREGNANCY, LACTATION and FERTILITY
Pregnancy
The safety of clarithromycin for use in pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risks.

Lactation
Clarithromycin is excreted into human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin.
The safety of clarithromycin use during breast-feeding of infants has not been established.

Fertility
In the rat, fertility studies have not shown any evidence of harmful effects.

OVERDOSAGE:
Symptoms
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, hypokalemia and hypoxemia.

Treatment
Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

CONTRAINDICATION:
- Hypersensitivity to macrolide antibiotic drugs or any of its excipients.
- Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, pimozide, terfenadine as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and *torsades de pointes*.
- Concomitant administration of clarithromycin and ergot alkaloids (e.g., ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity.
- Concomitant administration of clarithromycin and oral midazolam is contraindicated.
- Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including *torsades de pointes*.
- Clarithromycin should not be given to patients with electrolyte disturbances (hypokalemia or hypomagnesaemia, due to the risk of prolongation of the QT-interval).

- Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.
- Clarithromycin (and other strong CYP3A4 inhibitors) should not be used concomitantly with colchicine.
- As the dose cannot be reduced from 500 mg once-daily, clarithromycin modified release is contraindicated in patients with creatinine clearance less than 30 mL/min. Clarithromycin immediate release tablets may be utilized in this patient population.
- Concomitant administration with ticagrelor or ranolazine is contraindicated.
- Concomitant administration of clarithromycin and lomitapide is contraindicated

STORAGE CONDITIONS:
Store below 30°C. Protect from light and moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

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